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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 620 215 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **94302666.6**

(22) Date of filing : **14.04.94**

(51) Int. Cl.[5] : **C07D 209/22, C07D 209/24, C07D 401/06, A61K 31/405**

(30) Priority : **16.04.93 US 48629**
15.03.94 US 208721

(43) Date of publication of application :
19.10.94 Bulletin 94/42

(84) Designated Contracting States :
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

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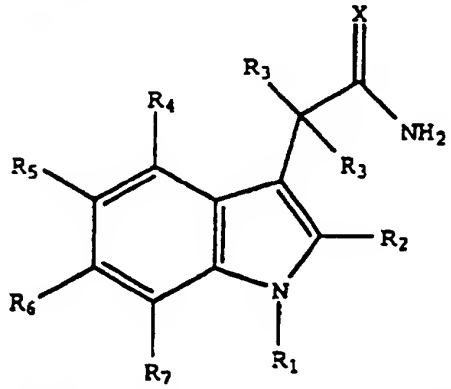
(54) 1H-Indole-3-acetamide derivatives as sPLA2 inhibitors.

(57) A class of 1H-indole-3-acetamides, represented by the formula (I), and pharmaceutically acceptable salts thereof ;



(I)

is disclosed together with the use of such indole compounds for inhibiting $sPLA_2$ mediated release of fatty acids for treatment of conditions such as septic shock.

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BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to novel 1H-indole-3-acetamides useful for inhibiting $sPLA_2$ mediated release of fatty acids for conditions such as septic shock.

Background Information

The structure and physical properties of human non-pancreatic secretory phospholipase A_2 (hereinafter called, "$sPLA_2$") has been thoroughly described in two articles, namely, "Cloning and Recombinant Expression of Phospholipase A_2 Present in Rheumatoid Arthritic Synovial Fluid" by Seilhamer, Jeffrey J.; Pruzanski, Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.; Kloss, Jean; and Johnson, Lorin K.; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5335-5338, 1989; and "Structure and Properties of a Human Non-pancreatic Phospholipase A_2" by Kramer, Ruth M.; Hession, Catherine; Johansen, Berit; Hayes, Gretchen; McGray, Peula; Chow, E. Pingcheng; Tizard, Richard; and Pepinsky, R. Blake; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5768-5775, 1989; the disclosures of which are incorporated herein by reference.

It is believed that $sPLA_2$ is a rate limiting enzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds which inhibit $sPLA_2$ mediated release of fatty acids (e.g.. arachidonic acid). Such compounds would be of value in general treatment of conditions induced and/or maintained by overproduction of $sPLA_2$; such as septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial esthma, allergic rhinitis, rheumatoid arthritis, and etc.

Indolyl-3 substituted compounds having glyoxylamide functionality are described in U.S. Patent 2,825,734. This patent related to a procese for converting glyoxyamides to 3-(2-amino-1-hydroxyethyl) indoles.

U.S. Patent No. 3,271,416 describes indolyl aliphetic acids as sun screening egents and intermediates. These acids may be $-NH_2$ substituted (see, definition of M in claim 1) and require 5- or 6- position substitution with nitrogen or sulfur functional groups.

U.S. Patent No. 2,890,223 and the article "The Synthesis of Tryptamines Related to Serotonin", by Elliott Shaw, J. Am. Chem. Soc., Vol. 77, 1955, (pp. 4319-4324) describe several amide derivatives of 3-indoleacetic acids. These compounds are used in the preparation of 5-lower alkoxy tryptaminee and are stated to have utility for influencing serotonin related functions in the brain. In addition, the article, "Recherches en serie indolique. VI sur tryptamines substituees", by Marc Julia, Jean Igolen and Henne Igolen, Bull. Soc. Chim. France, 1962, pp. 1060-1068, describes certain indole-3-acetamides and their conversion to tryptamine derivatives.

Selected indoyl emide type compounds heve been described in the literature for the treetment of arthritic disorders. Thus, U.S. Patents No. 3,196,162; 3,242,162; 3,242,163; and 3,242,193 (see, Col. 3, linea 55-60, Example 56) describe indolyl aliphatic acids together with their releted salts, esters, end amides . These compounds are closely releted to compounds like indomethacin, have e substituted benzyl group et the 1 position and likely echieve their beneficial action being cyclooxygenase inhibitors.

The article, "Some Analogs of 1-p-Chlorobenzyl-5-methylindole-3-acetic Acid", by E. Walton, et al., J. Med. Chem., Vol. 11, 1988, pp. 1252-1255, describes the preparation of isomeric methyl 3-(1-p-chlorobenzyl-5-methoxy-3-methylindole-2) propionete.

The article, "2-Aryl-3-Indoleecetamides (FGIN-1): A New Class of Potent and Specific Ligands for the Mitochondrial DBI Receptor (MDR)" by E. Romeo, et al. The Journal of Pharmacology and Experimental Therapeutics Vol. 262, No. 3, (pp. 971-978) describes certain 2-aryl-3-indolacetamides having research applications in mammalian central nervous systems.

It is desirable to develop new compounds end treatments for $sPLA_2$ induced diseases.

Summary of the Invention

This invention is a novel use of the class of compounds known es 1H-indole-3-ecetamides to inhibit humen $sPLA_2$ mediated release of fatty ecide.

This invention is also novel classes of 1H-indole-3-ecetamides having potent end selective effectiveness es inhibitors of human $sPLA_2$.

This invention is also pharmaceutical compositi ns containing the 1H-indole-3-ecetamides of the inv ntion.

This invention is also a method of preventing end treating e ptic eh ck using the 1H-indole-3-acetamides of the inv ntion.

Detailed Description of the Invention

Definitions:

The 1H-indole-3-acetamides of the invention employ certain defining terms as follows:

The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary butyl, isobutyl, sec-butyl, n-pentyl, and n-hexyl.

The term, "alkenyl" employed alone or in combination with other terms means a straight chain or branched monovalent hydrocarbon group having the stated number range of carbon atoms, and typified by groups such as vinyl, propenyl, crotonyl, isopentanyl, and various butenyl isomers.

The term, "halo" means fluoro, chloro, bromo, or iodo.

The term, "heterocyclic radical", refers to radicals derived from monocyclic or polycyclic, saturated or unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, furanyl, thiophanyl, pyrazolyl, imidazolyl, phanylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl, dibenzofuranyl, thianaphtheneyl, dibenzothiophanyl, indazolyl, imidazo(1.2-A)pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, banzoxazolyl, benzothiazolyl, purinyl, pryidinyl, dipyridylyl. phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl, quinazolinyl. quinoxalinyl.

The term, "carbocyclic radical" refers to radicals derived from a saturated or unsaturated, substituted or unsubstituted 5 to 14 membered organic nucleus whose ring forming atoms are solely carbon atoms Typical carbocyclic radicals are cycloalkyl, cycloalkenyl, phenyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, biphenyl, indenyl, acenaphthylenyl, and anthracanyl.

The term, "non-interfering substituent", refers to radicals suitable for substitution at positions 4, 5, 6, and/or 7 on the indole nucleus (as hereinafter depicted in Formula I) and radical(s) suitable for substitution on the heterocyclic radical and carbocyclic radical as defined above. Illustrative non-interfering radicals are C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_8 alkoxy, C_1-C_8 alkenyloxy, C_1-C_8 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_2-C_{12} alkylamino, C_1-C_8 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_8 alkylsulfinyl, C_1-C_8 alkylsulfonyl, C_1-C_8 haloalkoxy, C_1-C_8 haloalkylsulfonyl, C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, -C(O)O(C_1-C_8 alkyl), -$(CH_2)_n$-O-(C_1-C_8 alkyl), benzyloxy, phenoxy, phanylthio, (-CONHSO$_2$R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, -$(CH_2)_n$-CO_2H, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO_3H, thioacetal, thiocarbonyl, trifluoromathyl, and C_1-C_8 carbonyl; where n is from 1 to 8.

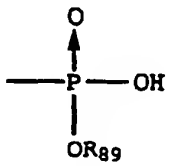
The term, "amine", includes primary, secondary and tertiary amines.

The term, "hydrocarbyl" means an organic group containing only carbon and hydrogen.

The term, "acidic group" means an organic group which when attached to an indole nucleus, through suitable connecting atoms, acts as a proton donor capable of hydrogen bonding. Illustrative of an acidic group are the following:

-5-tetrazolyl,

-SO_3H,



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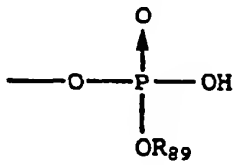

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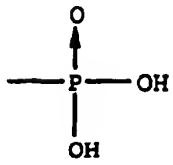

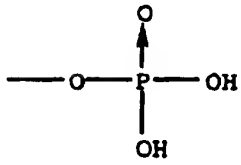

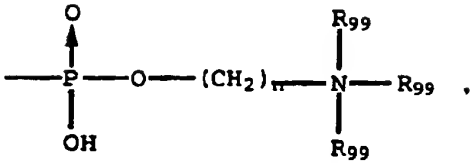

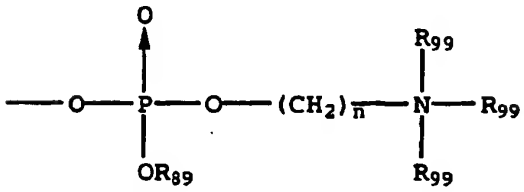

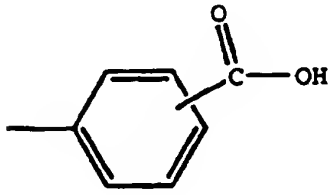

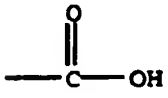

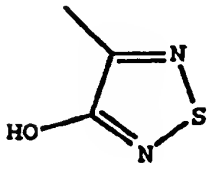

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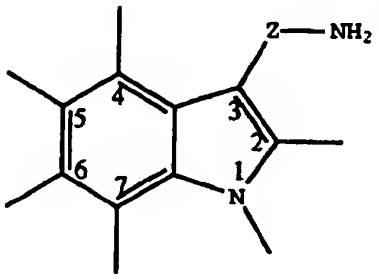
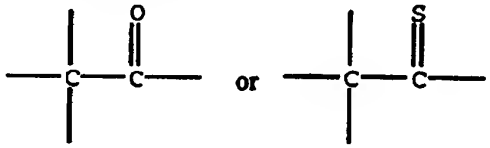
where n is 1 t 8, R_{89} is a metal or C_1-C_{10} alkyl, and R_{99} is hydrogen or C_1-C_{10} alkyl.

The compounds of the invention having utility for inhibiting human $sPLA_2$ mediated release of fatty acids are selected from "1H-indole-3-acetamides" having the general formula (A);



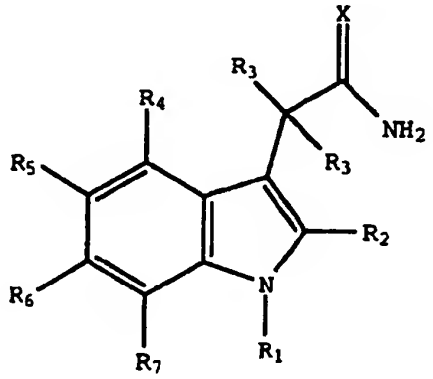
(A)

where Z is a divalent organic radical represented by



and the unsubstituted positions on the indolyl nucleus are independently satisfied by hydrogen or a non-interfering substituent. The indole nitrogen of formula (A) is preferably substituted by a $-(CH_2)_{1-6}$-(carbocyclic radical) or a $-(CH_2)_{1-6}$-(heterocyclic radical).

A preferred class of compounds according this invention are those having aryl, alkyl, haloalkyl, alkenyl, or alkynyl, groups on the indole nitrogen together with a relatively short (up to about 3 carbon atom size or equivalent) group at the 2-position (adjacent the indole nitrogen). Such 1H-indole-3-acetamides are represented by the formula (I), and pharmaceutically acceptable salts thereof;



(I)

wherein ;

X is oxygen or sulfur;

R_1 is selected from groups (i), (ii) and (iii) where;

(i) is C_6-C_{20} alkyl, C_6-C_{20} alkenyl, C_6-C_{20} alkynyl, C_6-C_{20} haloalkyl, C_4-C_{12} cycloalkyl, or

(ii) is selected from the group; ph nyl, naphthyl, indenyl, and biph nyl, where the members of the group are unsubstituted or substituted by the substituents halo, -CN, -CHO, -OH, nitro, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, C_1-C_{10} alkyl, carboxyl, amino, or hydroxyamino; or

(iii) is $-(CH_2)_n$-(R_{80}), or -(NH)-(R_{81}), where n is 1 to 8, and R_{80} is a group recited in (i), and R_{81} is selected

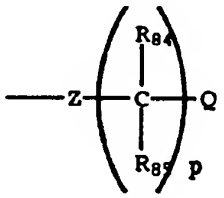
from a group recited in (i) or (ii);

R_2 is hydrogen, halo, C_1-C_3 alkyl, ethenyl, cyclopropyl, C_1-C_2 alkylthio, C_1-C_2 alkoxy, -CHO, or -CN;

each R_3 is independently hydrogen, halo, or methyl;

R_4, R_5, R_6, and R_7 are each independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in the set R_4, R_5, R_6, and R_7, combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN, C_1-C_{10} alkyl thio, arylthio, thioacetal, -C(O)O(C_1-C_{10} alkyl), hydrazide, hydrazino, hydrazido, $-NH_2$, $-NO_2$, $-NR_{82}R_{83}$, and $-C(O)NR_{82}R_{83}$, where, R_{82} and R_{83} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{82} and R_{83} form a 5 to 8 membered heterocyclic ring; or

a group having the formula;



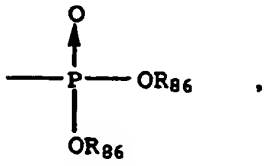
where,

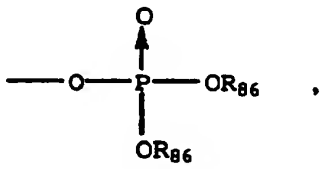
R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;

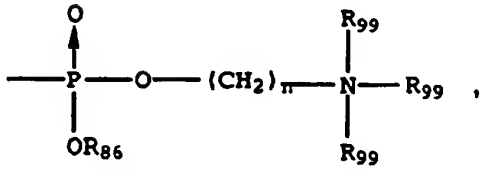
p is 1 to 5,

Z is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and

Q is $-CON(R_{82}R_{83})$, -5-tetrazolyl, $-SO_3H$,







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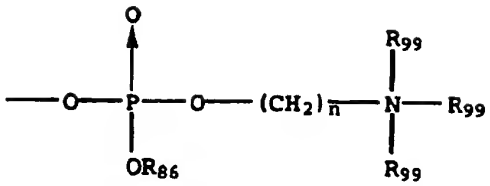
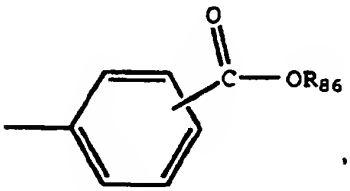
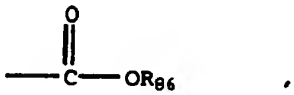
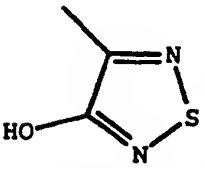


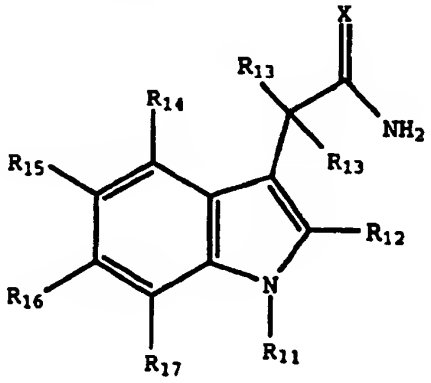






where n is 1 to 8, R_{86} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

Another preferred class of indoles according to this invention are those having alkyl, aryl, or benzyl groups or their derivatives on the indole nitrogen. Such 1H-indole-3-acetamides are represented by the formula (II), and pharmaceutically acceptable salts thereof,



(II)

wherein ;

X is oxygen or sulfur;

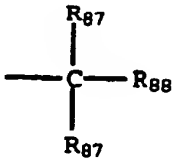
R_{11} is selected from groups (i), (ii) (iii) and (iv) where;

(i) is C_6-C_{20} alkyl, C_6-C_{20} alkenyl, C_6-C_{20} alkynyl, C_6-C_{20} haloalkyl, C_4-C_{12} cycloalkyl, or

(ii) is aryl r aryl substituted by halo, nitro, -CN, -CHO, -OH, -SH, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, carboxyl, amino, or hydroxyamino; or

(iii) is $-(CH_2)_n-(R_{80})$, or $-(NH)-(R_{81})$, where n is 1 to 8, and R_{80} is a group recited in (i), and R_{81} is selected from a group recited in (i) or (ii);

(iv) is

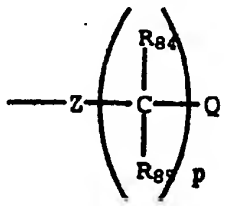


where R_{87} is hydrogen or C_1-C_{10} alkyl, and R_{88} is selected from the group; phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, phenyl, nitro, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, carboxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

R_{12} is halo, C_1-C_2 alkylthio. or C_1-C_2 alkoxy;

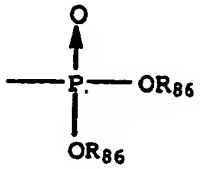
each R_{13} is independently hydrogen, halo, or methyl;

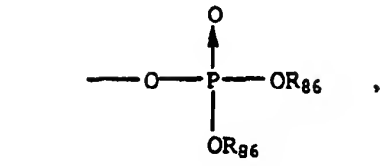
R_{14}, R_{15}, R_{16}, and R_{17} are each independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in the set R_{14}, R_{15}, R_{16}, and R_{17}, combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN, C_1-C_{10} alkylthio, arylthio, thioacetal, $-C(O)O(C_1$-C_{10} alkyl), hydrazide, hydrazino, hydrazido, $-NH_2$, $-NO_2$, $-NR_{82}R_{83}$, and $-C(O)NR_{82}R_{83}$, where, R_{82} and R_{83} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{82} and R_{83} form a 5 to 8 membered heterocyclic ring; or a group having the formula;

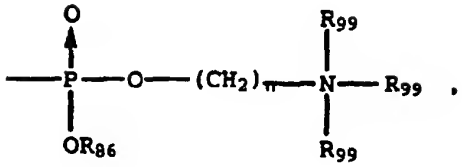


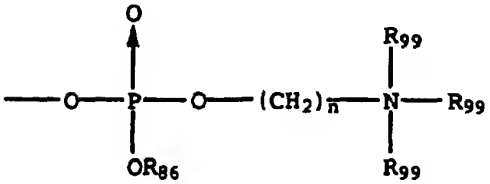
where,

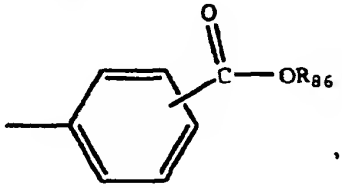
R_{84} and R_{85}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, $-N(C_1$-C_{10} alkyl)-, -NH-, or -S-; and
Q	is $-CON(R_{82}R_{83})$, -5-tetrazolyl, $-SO_3H$,

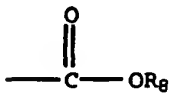


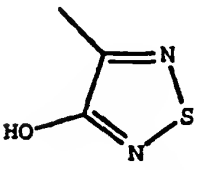






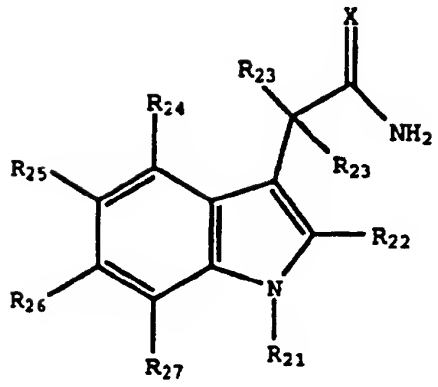






where n ie from 1 to 8, R_{86} ie independently eelected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is eelected from hydrogen or C_1-C_{10} alkyl.

Another preferred group of Indoles according to this invention are those having two key substituents; namely, (1) an acidic group at one or both the 4 or 5 positions (viz., R_{24} and R_{25} as depicted in formula III), and (2) a benzyl or substituted benzyl group on the ind l nitrogen. Such 1H-Indole-3-acetamid s are represented by the formula (III), and pharmaceutically acceptabl salts thereof,



(III)

wherein ;

X is oxygen or sulfur;

R_{21} is $-(CH_2)_n-(R_{80})$, or $-(NH)-(R_{80})$, where n is 1 to 8, and R_{80} is aryl or aryl substituted by C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_4-C_{12} cycloalkyl, C_1-C_{10} hydroxyalkyl, carboxyl, halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, carboxyl, amino, or hydroxyamino, or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

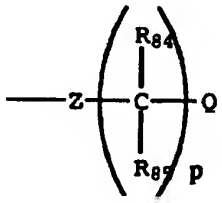
R_{22} is hydrogen, halo, C_1-C_3 alkyl, ethenyl, cyclopropyl, C_1-C_2 alkylthio, C_1-C_2 alkoxy, -CHO, -CN;

each R_{23} is independently hydrogen, halo, or methyl;

R_{24} and R_{25} are each independently selected from (a) and (b) where;

(a) is hydrogen, halo, alkyl, or alkoxy, and;

(b) is a group having the formula;



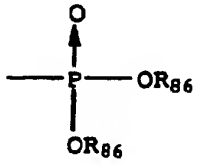
with the proviso that at least one of R_{24} and R_{25} must be selected from (b), and where;

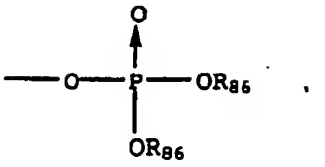
R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;

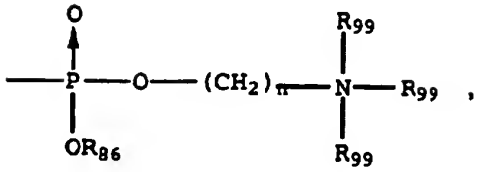
p is 1 to 5,

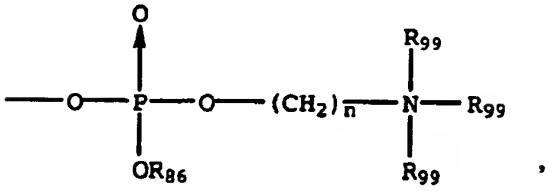
Z is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and

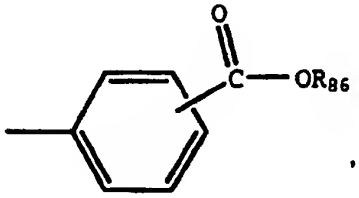
Q is $-CON(R_{82}R_{83})$, -5-tetrazolyl, $-SO_3H$,

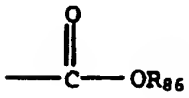


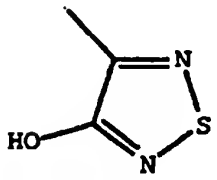








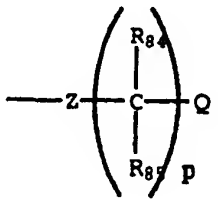




where n is 1 to 8, R_{86} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

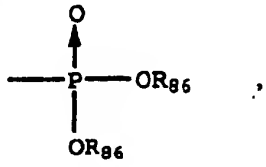
R_{26}, and R_{27} are each independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alk nyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or the adjacent hydrocarbyl groups In the groups R_{26} and R_{27} combine with the ring carbon atoms to which th y are attached to form a 5 r 6 membered substituted r unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} hal alkoxy, C_4-C_8 cycloalkoxy, phenoxy, hal , hydroxy, carboxyl, -SH,

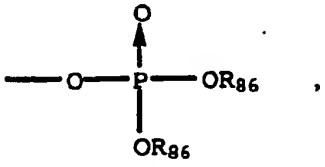
-CN, C_1-C_{10} alkylthio, arylthi , thioacetal, -C(O)O(C_1-C_{10} alkyl), hydrazide, hydrazin , hydrazido, $-NH_2$, $-NO_2$, $-NR_{82}R_{83}$, and $-C(O)NR_{82}R_{83}$, where, R_{82} and R_{83} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{82} and R_{83} form a 5 to 8 membered heterocyclic ring; or
a group having the formula;

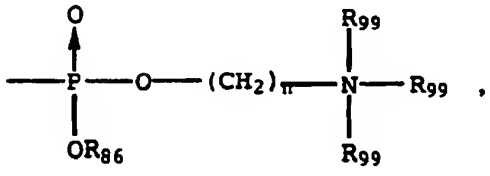


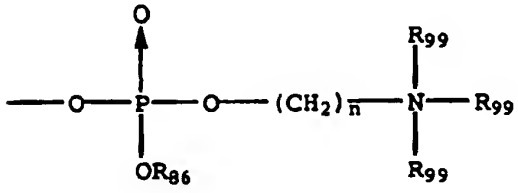
where,

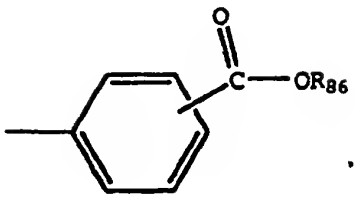
R_{84} and R_{85}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, $-N(C_1$-C_{10} alkyl)-, -NH-, or -S-; and
Q	is $-CON(R_{82}R_{83})$, -5-tetrazolyl, $-SO_3H$,

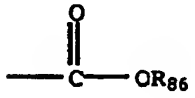


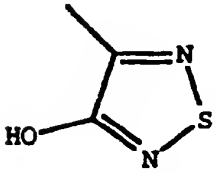






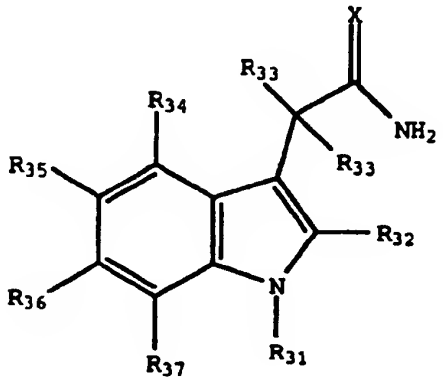






where n is 1 to 8, R_{88} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

Another preferred class of indoles according to this invention are those having two key substituents; namely, (1) an acidic group at one or both the 4 or 5 positions (viz., R_{34} and R_{35} as depicted in formula IV, and (2) a small substituent containing halogen, sulfur, or oxygen at the 2-position of the indole ring (R_{32} of formula IV). Such 1H-Indole-3-acetamides are represented by the formula (IV), and pharmaceutically acceptable salts thereof,



(IV)

wherein ;

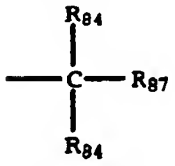
X is oxygen or sulfur;

R_{31} is selected from groups (i), (ii) and (iii) where;

(i) is C_6-C_{20} alkyl, C_6-C_{20} alkenyl, C_6-C_{20} alkynyl, C_6-C_{20} haloalkyl, C_4-C_{12} cycloalkyl, or

(ii) is aryl or aryl substituted by halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, carboxyl, amino, or hydroxyamino;

(iii) is



where R_{84} is hydrogen or C_1-C_{10} alkyl, and R_{87} is selected from the group: phenyl, naphthyl, indanyl and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxy, carboxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

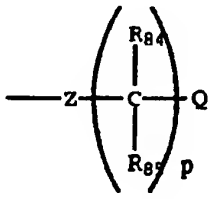
R_{32} is halo, C_1-C_2 alkylthio, C_1-C_2 alkoxy;

each R_{33} is independently hydrogen, halo, or methyl;

R_{34} and R_{35} are each independently selected from (a) and (b) where;

(a) is hydrogen, halo, alkyl, or alkoxy, and

(b) is a group having the formula;



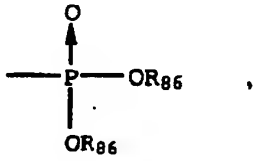
with the proviso that at least one of R_{34} and R_{35} must be selected from (b), and where;

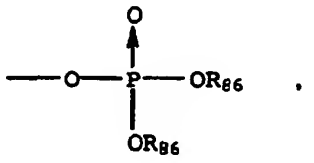
R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;

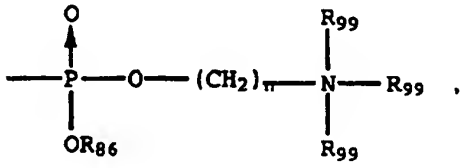
p is 1 to 5,

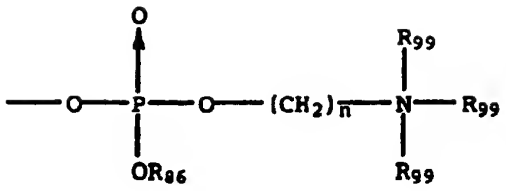
Z is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and

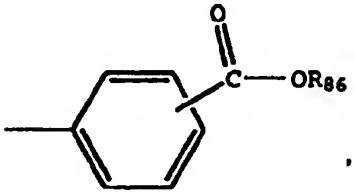
Q is -CON($R_{82}R_{83}$), -5-tetrazolyl, -SO_3H,

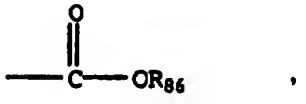


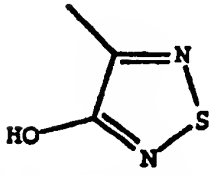






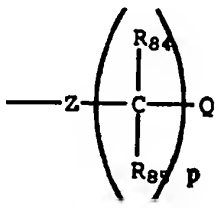






where n is 1 to 8, R_{88} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

R_{36}, and R_{37} are each independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or the adjacent hydrocarbyl groups in the groups R_{36} and R_{37} combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN, C_1-C_{10} alkylthio, arylthio, thioacetal, -C(O)O(C_1-C_{10} alkyl), hydrazide, hydrazino, hydrazido, $-NH_2$, $-NO_2$, $-NR_{82}R_{83}$, and $-C(O)NR_{82}R_{83}$, where, R_{82} and R_{83} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{82} and R_{83} form a 5 to 8 membered heterocyclic ring; or
a group having the formula;



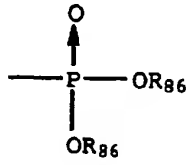
where,
R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken

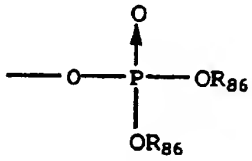
together are =O;

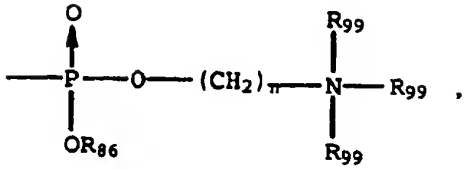
p is 1 to 5,

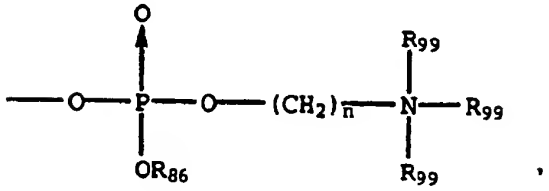
Z is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and

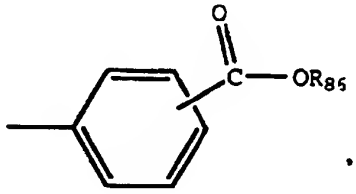
Q is -CON($R_{82}R_{83}$), -5-tetrazolyl, -SO_2H,

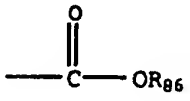


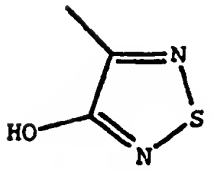








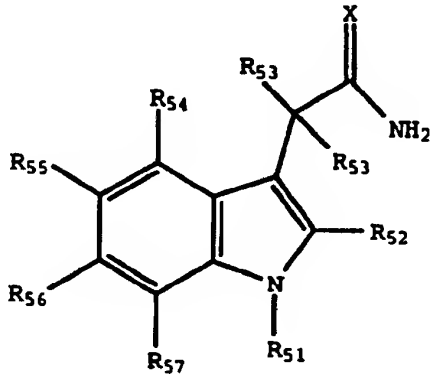




;

where n is 1 to 8, R_{88} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

A most preferred class of indole compounds according to this invention are those wherein X is oxygen in formula V, the nitrogen of the indole ring is substituted by a benzyl or biphenyl methyl group, and the 2-position on the indole ring (viz., R_{52} in formula V) is substituted with either halo, methylthio, or C_1-C_3 alkyl. Such 1H-indole-3-acetamides are represented by the formula (V), and pharmaceutically acceptable salts thereof,

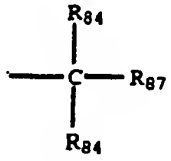


(V)

wherein;

X is oxygen;

R_{51} is



where,

R_{84} is hydrogen or C_1-C_{10} alkyl, and R_{87} is $-(CH_2)_m$-(phenyl) or $-(CH_2)_m$-(biphenyl), wherein m is 0 to 2 and the phenyl or biphenyl radicals are unsubstituted or substituted by halo, -CN, -CHO, -OH, nitro, phenyl, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkyl, C_1-C_{10} alkoxyl, carboxyl, amino, hydroxyamino or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

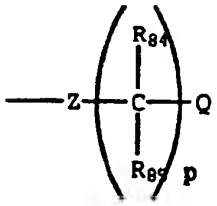
R_{52} is halo, methylthio, cyclopropyl, or C_1-C_3 alkyl;

each R_{53} is hydrogen or halo;

R_{54} and R_{55} are each independently selected from (a) and (b) where;

(a) is hydrogen, and;

(b) is a group having the formula;



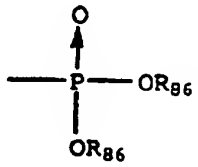
with the proviso that at least one of R_{54} and R_{55} must be selected from (b), and where;

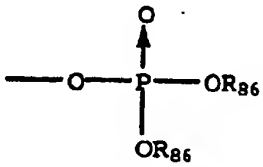
R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;

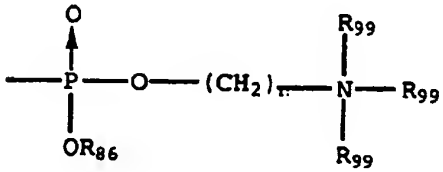
p is 1 to 5,

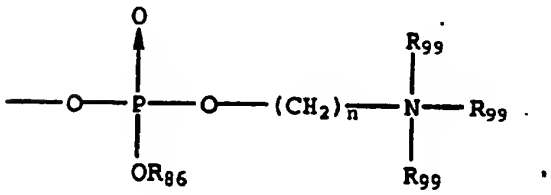
Z is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH- or -S-; and

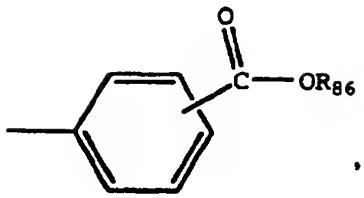
Q is -5-tetrazolyl, $-SO_3H$,

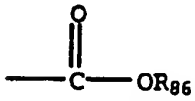






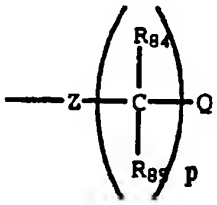






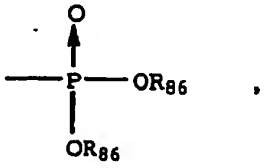
where n is 1 to 8, R_{88} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

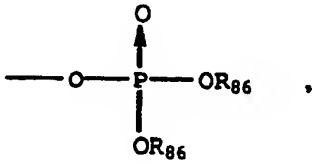
R_{56}, and R_{57} are each independently hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, phenoxy, halo, hydroxy, carboxyl, or a group having the formula;

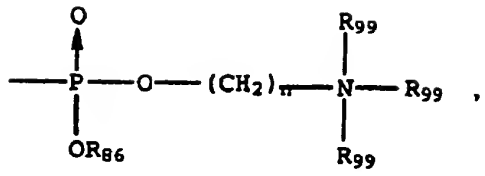


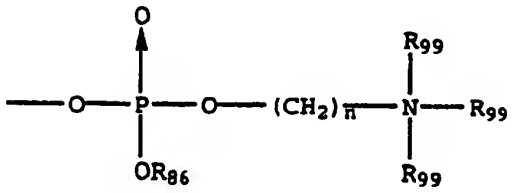
where,

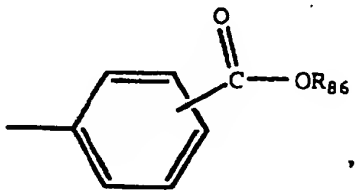
R_{84} and R_{85}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and
Q	is -5-tetrazolyl, -SO_3H,

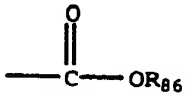








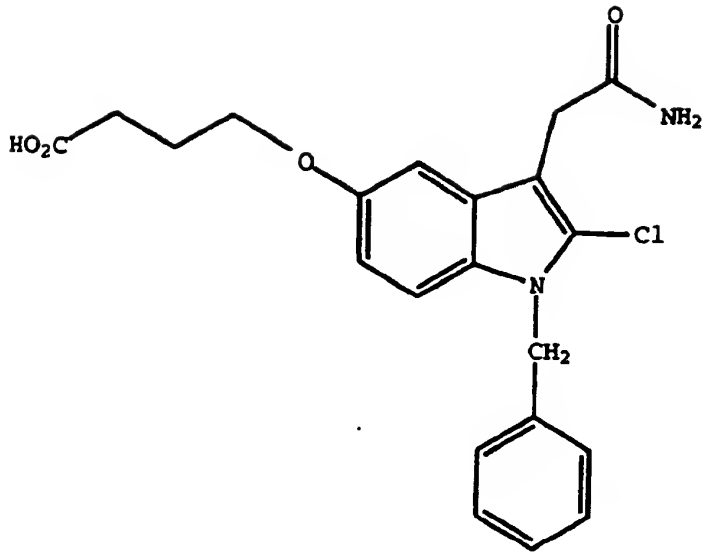




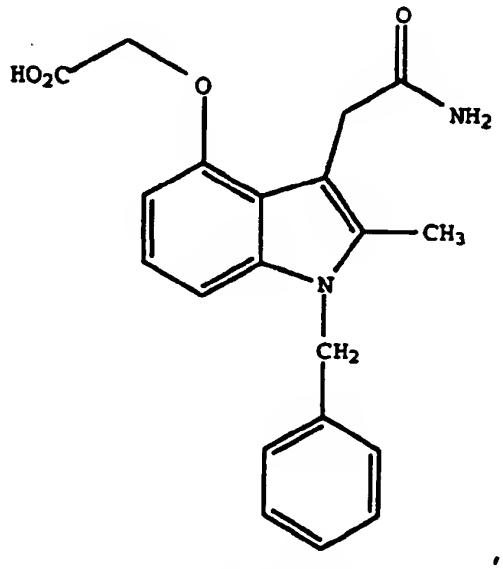
where n is 1 to 8, R_{88} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

Illustrative of the novel compounds having utility in this invention are the following:

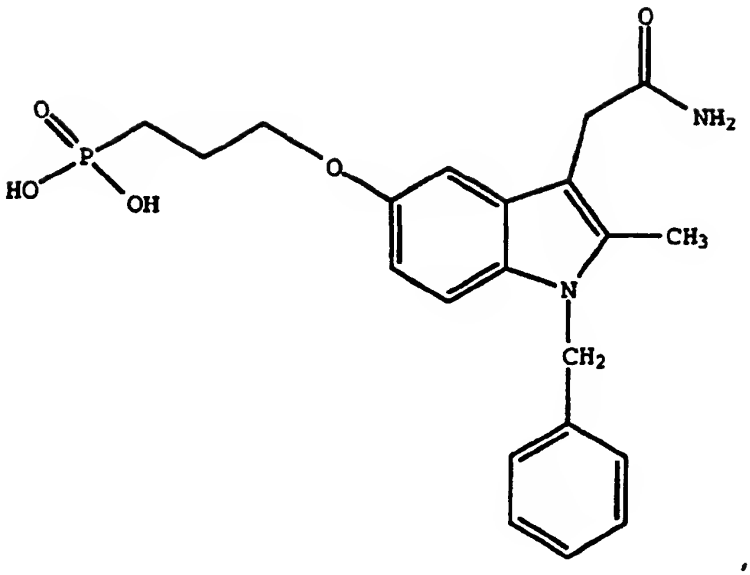
4-[[3-(2-Amino-2-oxoethyl)-2-chloro-1-(phenylmethyl)-1H-indole-5-yl]oxy]butanoic acid, a compound represented by the formula:



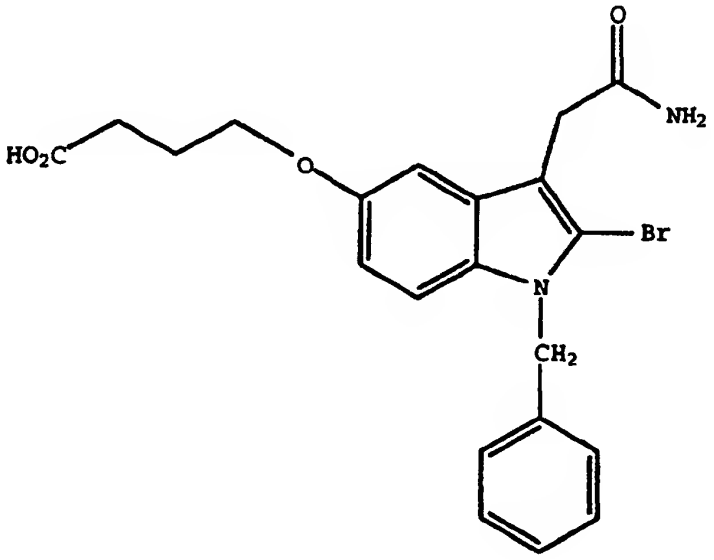
2-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid, a compound represented by the formula:



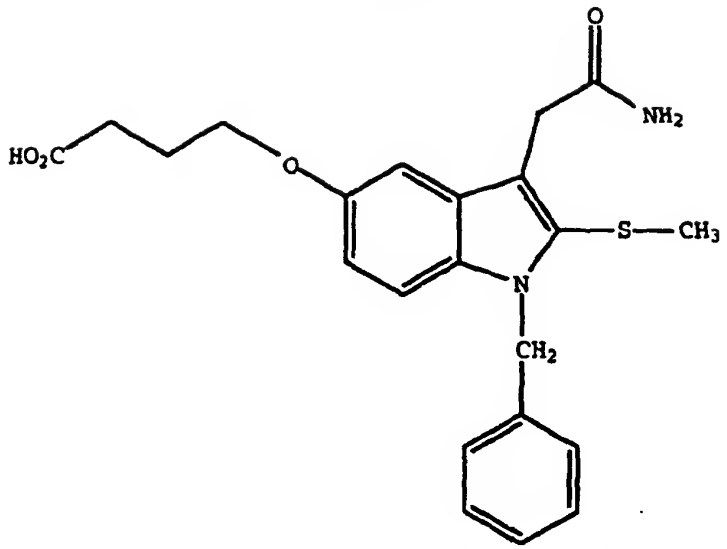
[3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid, a compound represented by the formula:



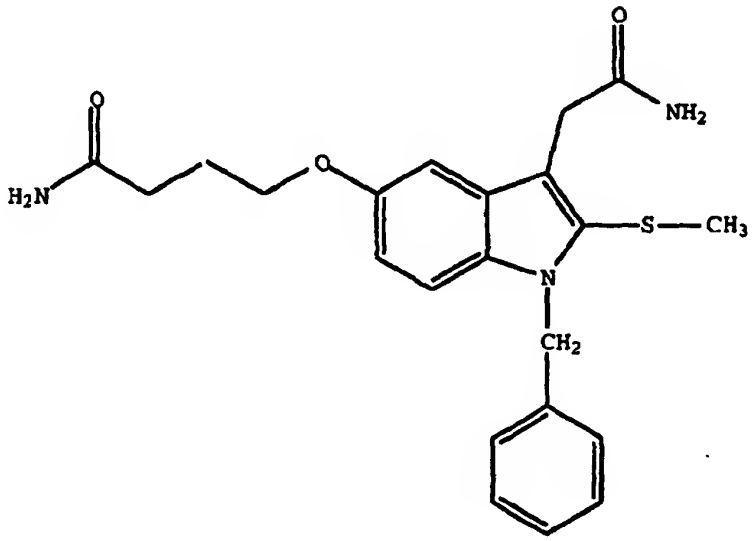
4-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid, a compound represented by the formula:



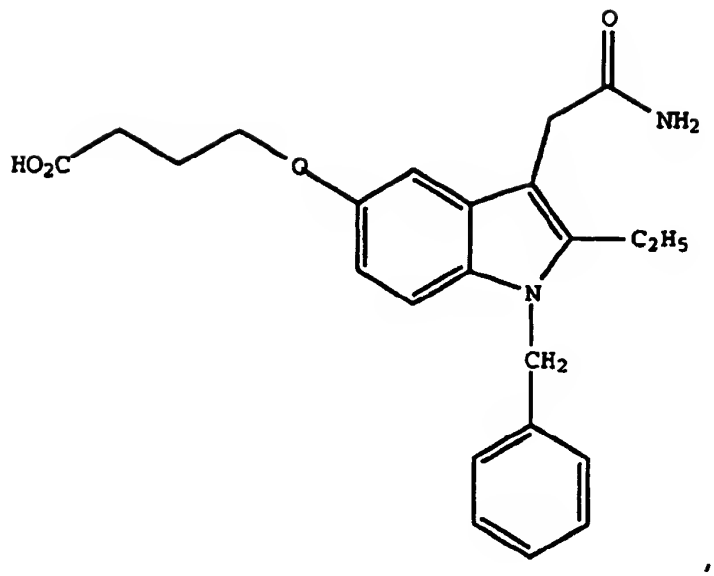
4-[[3-(2-Amino-2-oxoethyl)-2-(methylthio)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid, a compound represented by the formula:



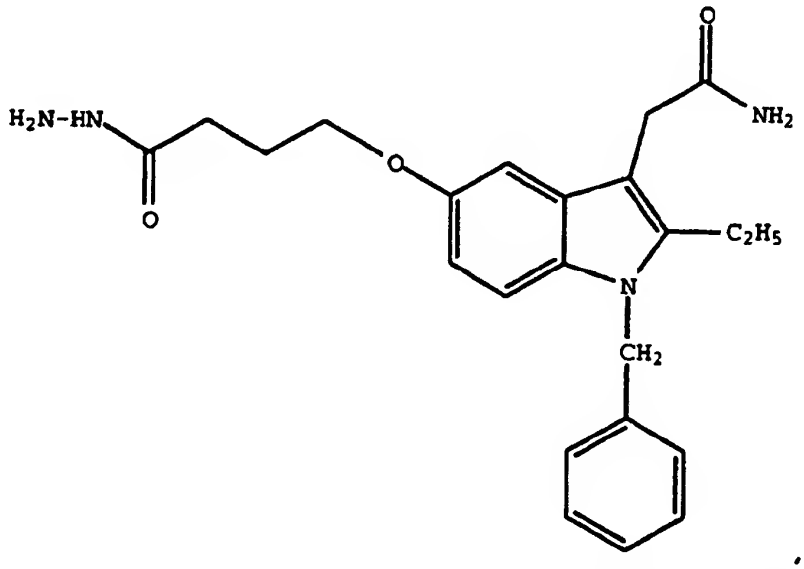
5-(4-Amino-4-oxobutoxy)-2-(methylthio)-1-(phenylmethyl)-1H-indole-3-acetamide, a compound represented by the formula:



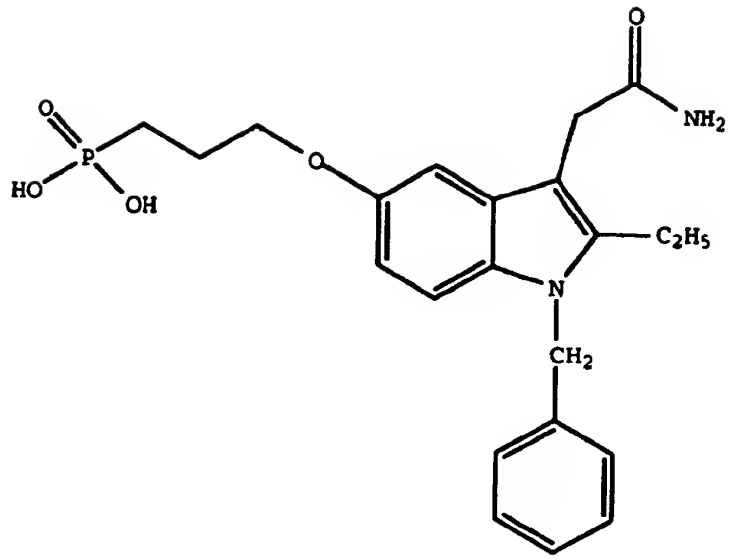
[4-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1-H-indol-5-yl]oxy]butanoic acid, a compound represented by the formula:



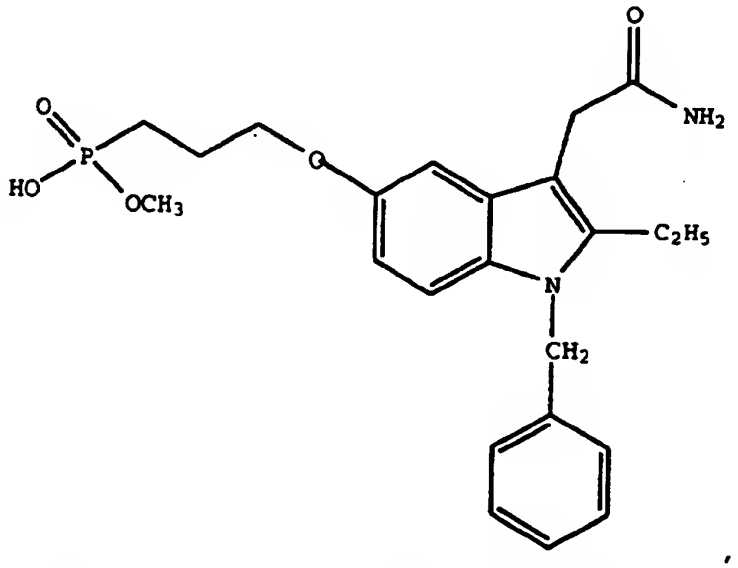
2-Ethyl-5-(4-hydrazino-4-oxobutoxy)-1-(phenylmethyl)-1H-indole-3-acetamide, a compound represented by the formula:



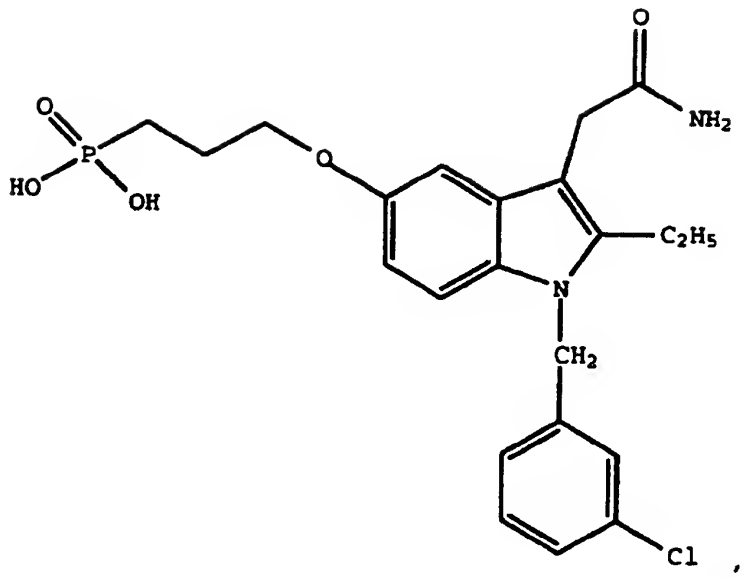
[3-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid, a compound represented by the formula:



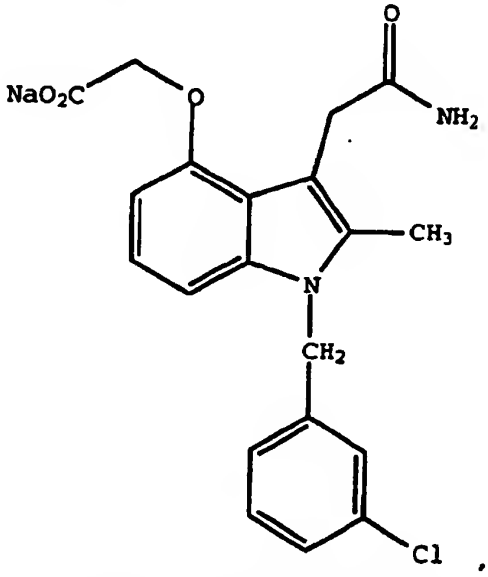
[3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid monomethyl ester, a compound represented by the formula:



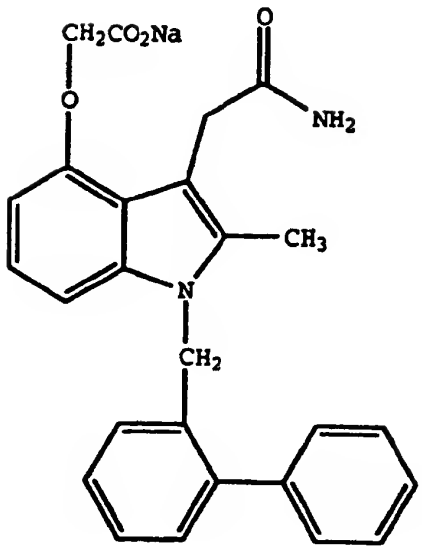
[3-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl 1H-indol-5-yl]oxy]propyl]phosphonic acid, a compound represented by the formula:



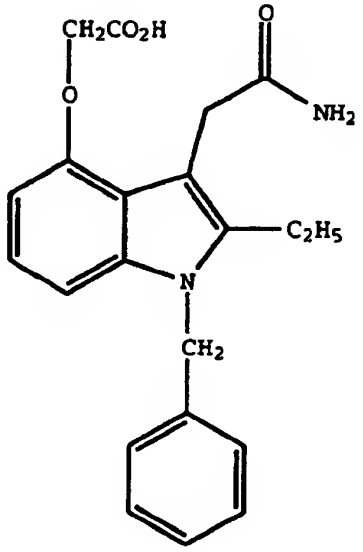
[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]methyl]acetic acid sodium salt, a compound represented by the formula:



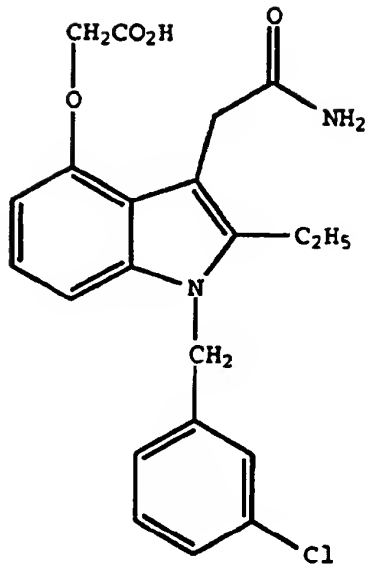
[[3-(2-Amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid sodium salt, a compound represented by the formula:



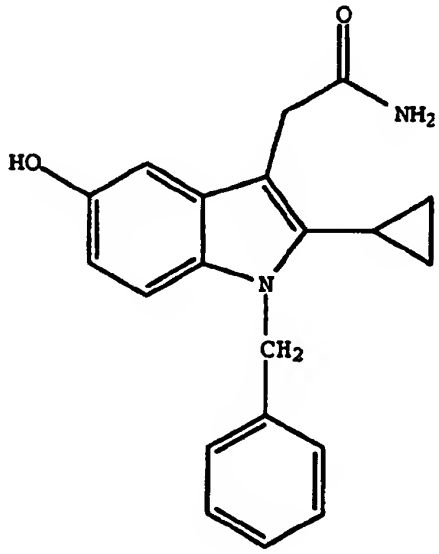
[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid, a compound represented by the formula:



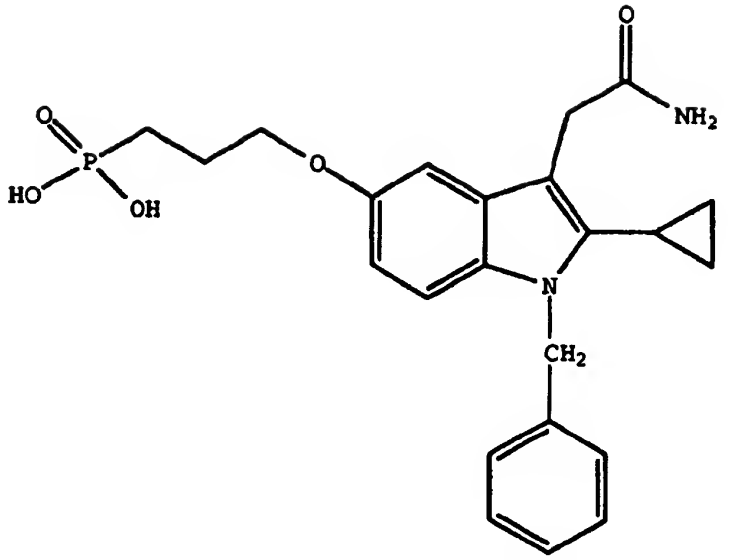
2-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid, a compound represented by the formula:



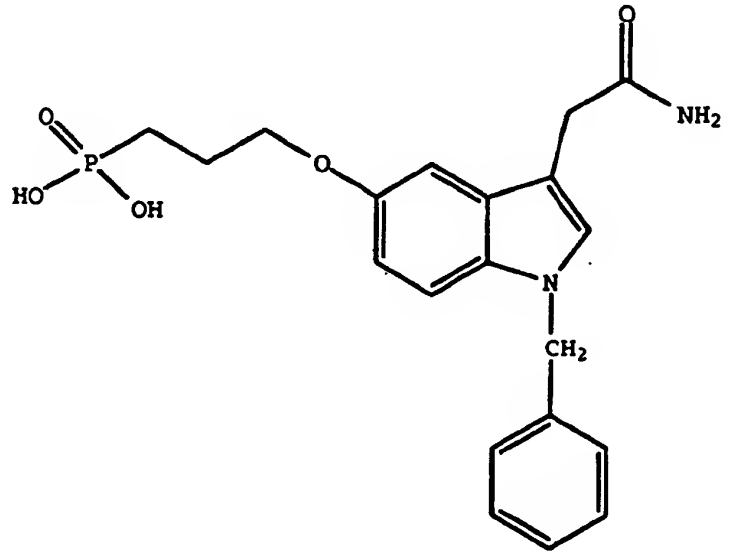
2-Cyclopropyl-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide, a compound represented by the formula:



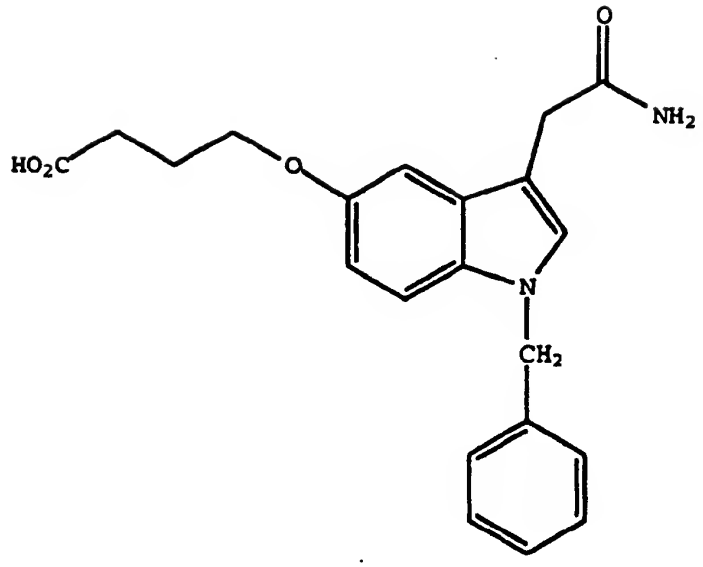
[3-[[3-(2-Amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid, a compound represented by the formula:



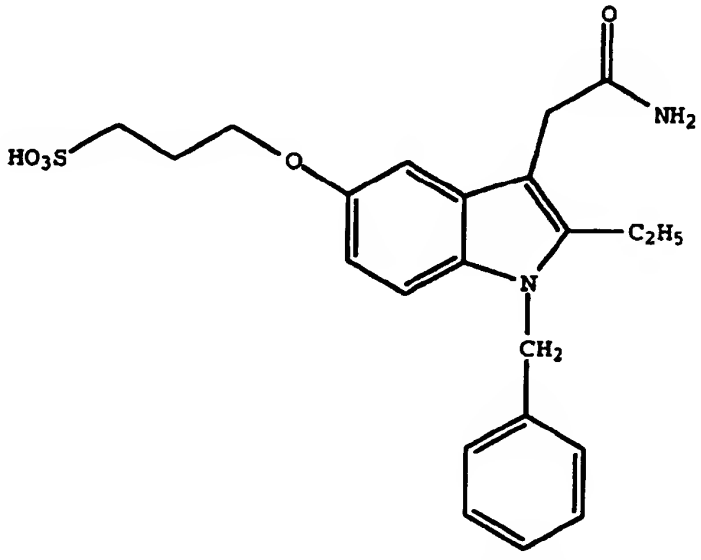
[3-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid, a compound represented by the formula:



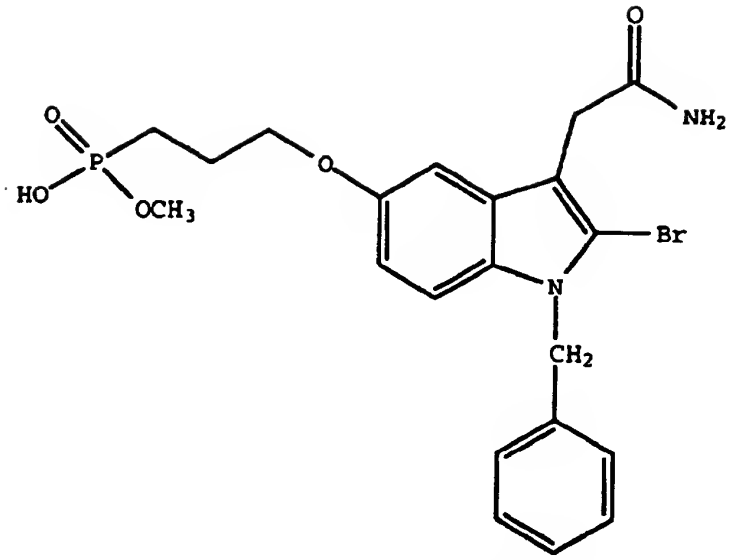
4-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid, a compound represented by the formula:



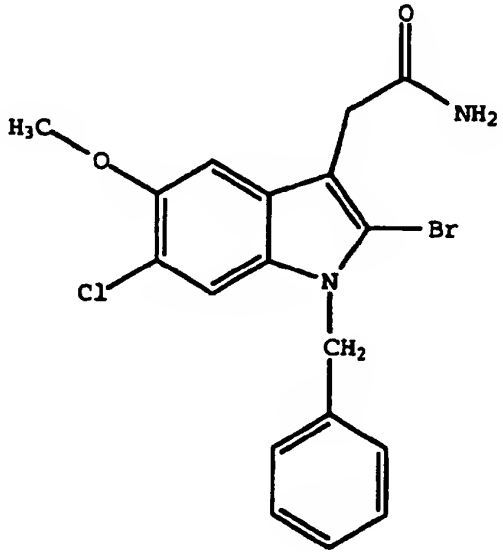
3-[4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propane]sulfonic acid, a compound represented by the formula:



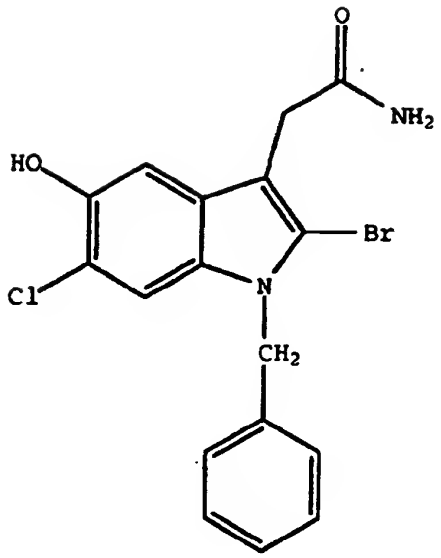
3-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid monomethyl ester, a compound represented by the formula:



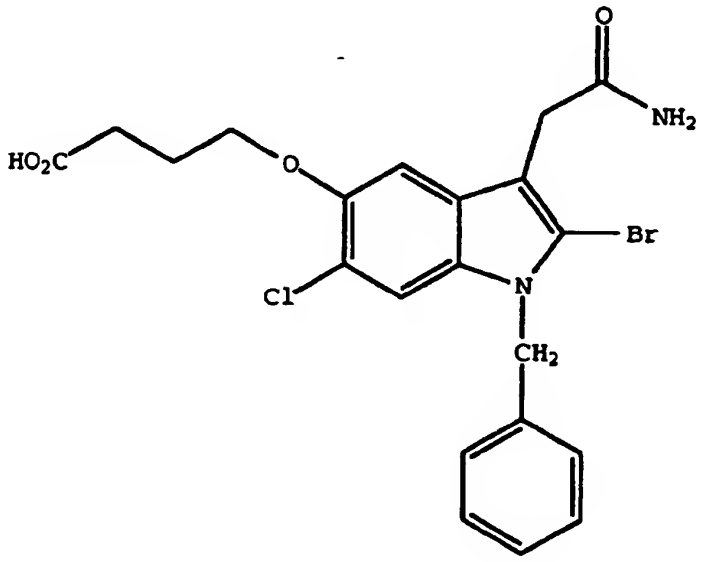
2-Bromo-6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetamide, a compound represented by the formula:



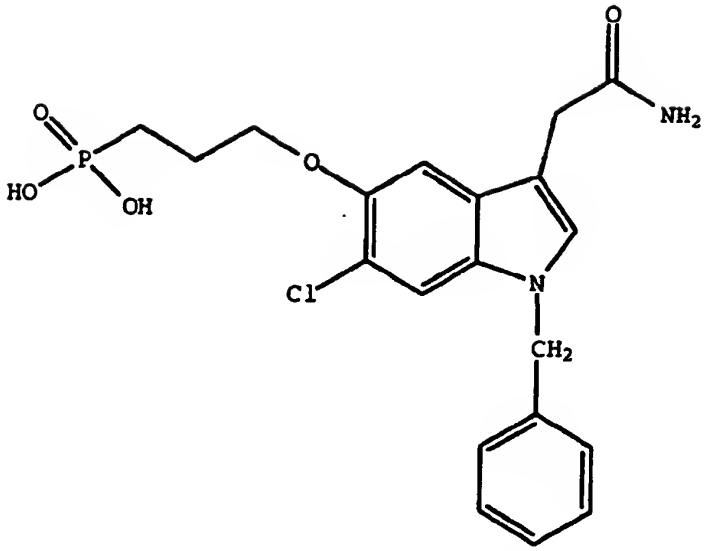
2-Bromo-6-chloro-5-hydroxy-1-(phenylmethyl)-H-indole-3-acetamide, a compound represented by the formula:



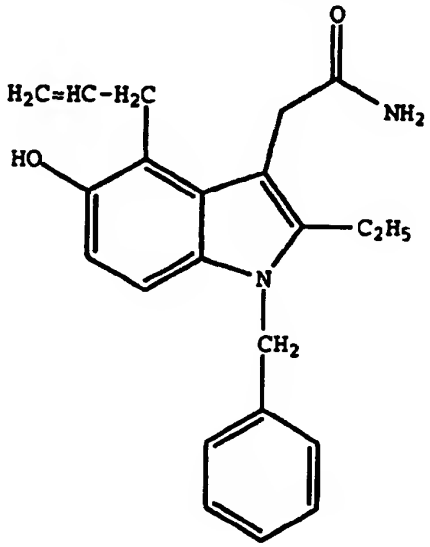
4-[[3-(2-Amino-2-oxoethyl)-2-bromo-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid, a compound represented by the formula:



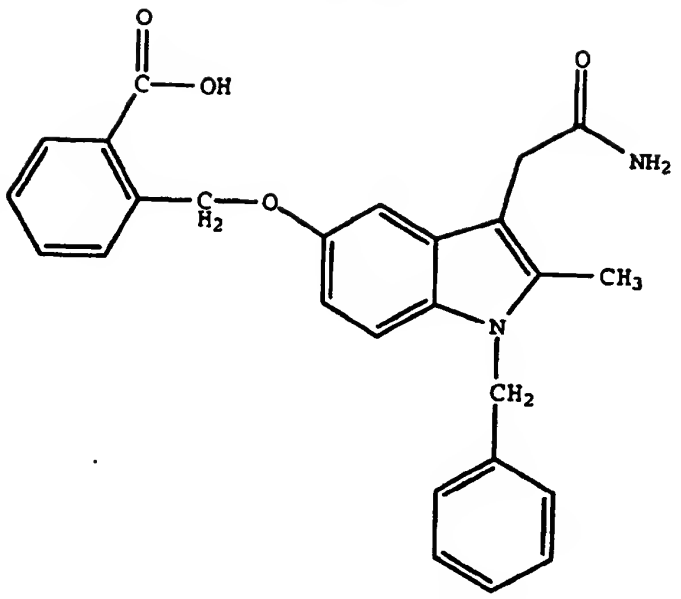
3-[4-[[3-(2-Amino-2-oxoethyl)-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid, a compound represented by the formula:



4-Allyl-2-ethyl-5-hydroxy-1-(phenylmethyl)-1H-indole-acetamide, a compound represented by the formula:



2-[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid, a compound represented by the formula:



and pharmaceutically acceptable salts of each of the above named compounds.

The salts of the above 1H-indole-3-acetamide compounds of formulae A, I, II, III, IV, V, VI and the above named specific compounds are an additional aspect of the invention. In those instances where the compounds of the invention possess acidic or basic functional groups various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts. Include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases (e.g., derived from glucosamine, morpholine, choline, or diethylamine) of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, chloride, edetate, edisylate, estolate, esylate, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, bromide, chloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or more chiral centers and may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of cis- and trans- isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue com-

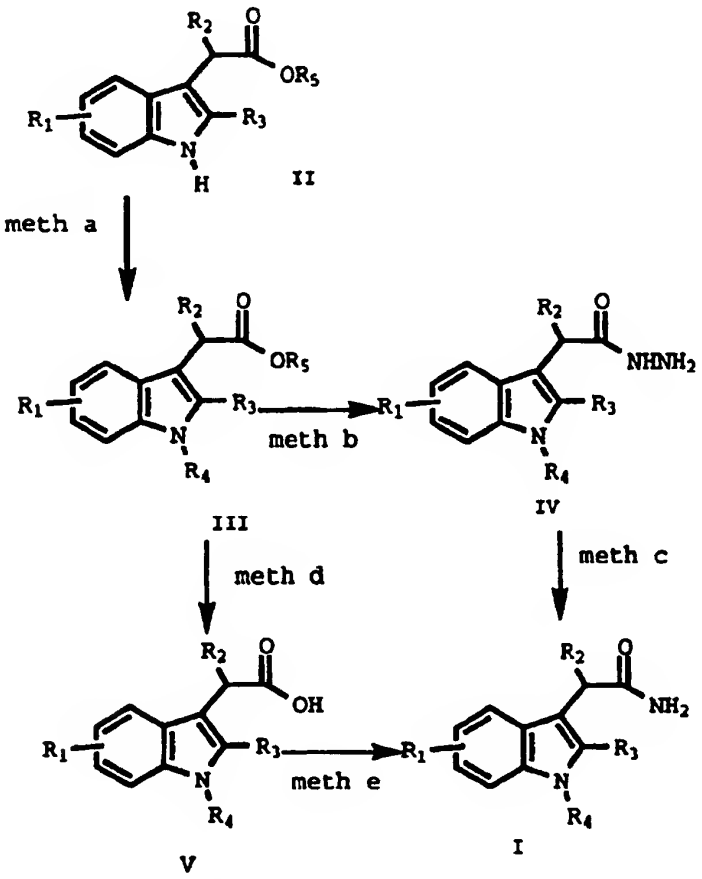
patibility, or delayed release in a mammalian organism (see, Bundgard, H., Design f Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters.

Synthesis Methods

The synthesis of the 1H-indole-3-acetamides of structure (I) can be accomplished by known methods. Procedures useful for the syntheses of the compounds of this invention are outlined in the following reaction schemes:

In the first scheme, the 1H-indole-3-acetic acid esters, II, can be readily

Scheme 1.

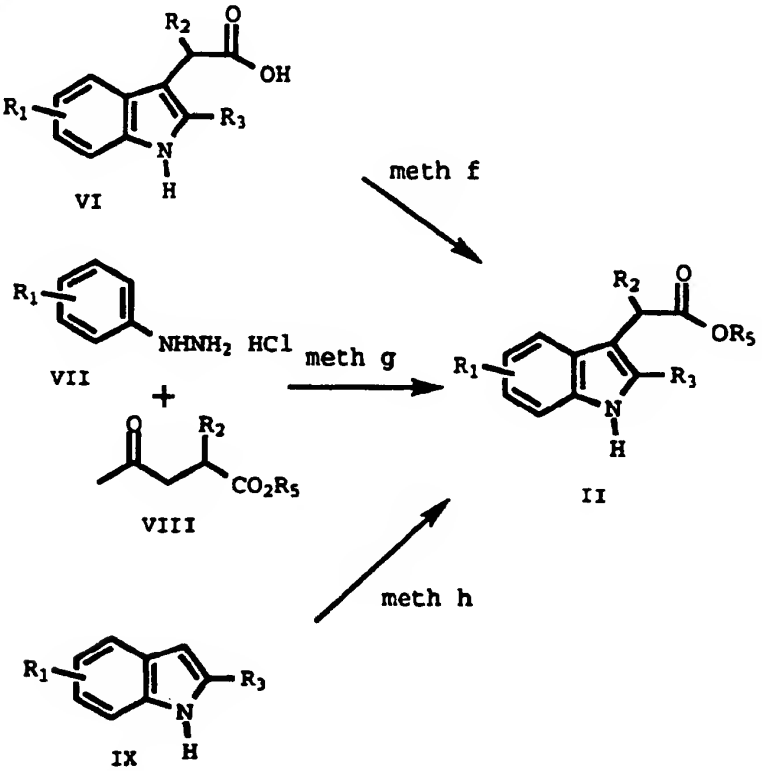


alkylated by an alkyl halide or arylalkyl halide in a solvent such as N,N-dimethylformamide (DMF) in the presence of a base (method a) to giv Intermediate 1-alkyl-1H-indole-3-acetic acid esters, III. Bases such as potassium t-butoxide and sodium hydride are useful. It is advantageous to react th Indole, II, with the bas to first form the salt of II and then add alkylating agent. Treatment of the 1-alkyl-1H-indole-3-acetic acid esters, III, with hydrazine or hydrazine hydrate In thanol (method b) gives th desired 1-alkyl-1H-indole-3-acetic acid hydrazid s, IV. This condensation to form IV may be carried out at the reflux temperature of the solvent for a

period of 1 to 24 hours. The acetic acid hydrazides, IV, are hydrogenated to give the acetamides, I, by heating with Raney nickel in athanol (method c). The intermediate acetic acid esters, III, can be first hydrolyzed to the acetic acid derivatives, V (method d), which on treatment with an alkyl chloroformate followed by anhydrous ammonia, also give amides, I (method a).

The intermediate 1H-indole-3-acetic acid esters, II, can be obtained from several synthatic routes as illustrated in Schame 2. The 1H-indole-3-acetic acids, VI, are readily esterified in an alcohol such as methanol in the

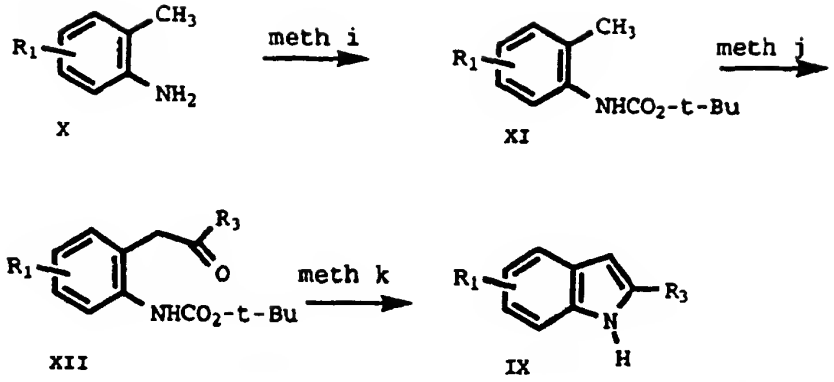
Scheme 2



presence of a strong acid, such as sulfuric acid (method f) to give II. Substituted phenylhydrazines, VII, can be reacted with levulinic acid derivatives, VIII, by the well known Fisher-indola synthesis (method g) to give (see, ref. B. Carlin and E. E. Fisher, J. Am. Chem. Soc., 1948, *70*, 3421) directly the indola, II. Ethanol as solvent at reflux temperature and hydrogen chloride as the acid catalyst is generally used. Indoles that are unsubstituted at the 3-position, IX, can be alkylated by first forming the zinc salts of IX and treating these salts with alkyl 2-bromoalkanoate (see, ref. Yoshihiko Ito, Hideaki Sato, Masahiro Murakami, J. Org. Chem., 1991, *56*, 4864-4867) in (method h) to give II. The zinc salts of IX can be prepared by reacting the indoles IX first with n-butyllithium using tetrahydrofuran as solvent and then with zinc chloride in ether. The solvent for this reaction is usually changed after the zinc salt formation to toluene by removing the ether and THF solvent at reduced pressure and adding toluene.

For additional substituted derivatives of IX, the reactions in Scheme 3 are (see, ref. Robin D. Clark, Joseph M. Muchowski, Lawrence E. Fisher, Lee A. Flippin, David B. Repke, Michel Souchet, Synthesis, 1991, 871-878) employed.

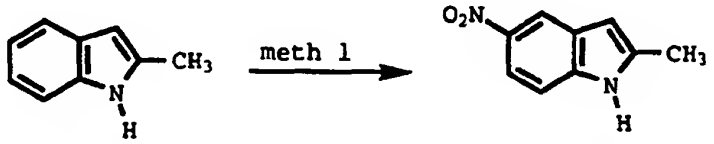
Scheme 3.



X XI XII IX

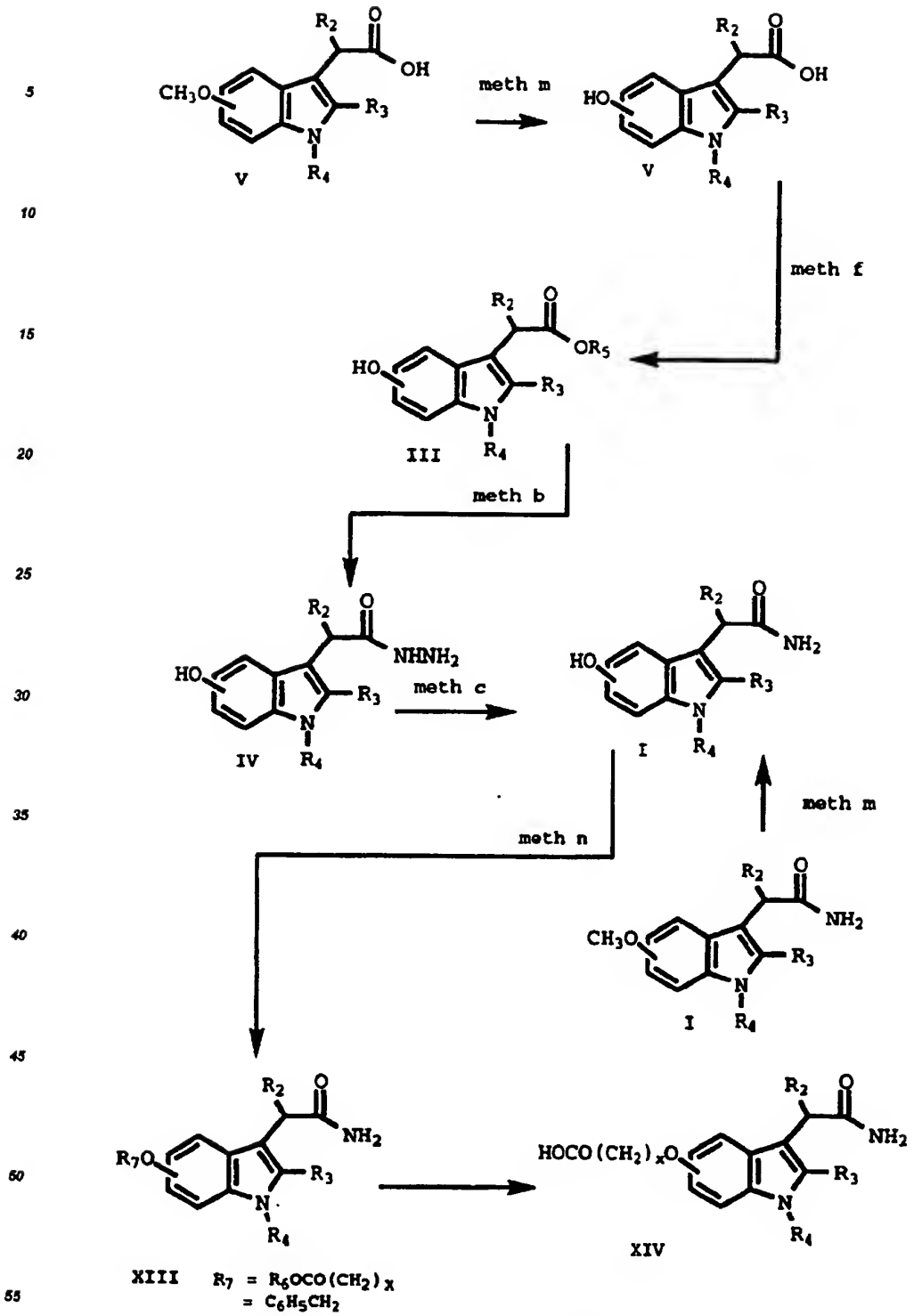
Ortho-methylanilines, X, are treated with di-*tert*-butyl dicarbonate in THF at reflux temperature (method i) to give the N-*tert*-butoxycarbonylanilines, XI. The dianion of XI is formed in THF by treatment with two equivalents of *sec*-butyl lithium and reacts with one equivalent of an N-methoxy-N-methylalkanoic acid amide to give (method J) the aryl ketone, XII. These ketones on treatment with trifluoroacetic acid (method k) are both cyclized and deprotected on the nitrogen to give the indoles, IX. Indoles of type IX that are substituted at the 5-position with nitro, are (see, ref. Wayland E. Noland, Lowell R. Smith, and Donald C. Johnson, J. Org. Chem., 1963, *28*, 2262-2266) obtained by adding sodium nitrate to the appropriate indole previously dissolved in sulfuric acid (method l).

Scheme 4.



To obtain derivatives of I where the R_1 substituent is 5-hydroxy or an alkoxy other than methoxy, the methods described in scheme 5 are used. The 5-methoxy indole-3-acetic acids are readily demethylated (method m) by treatment with BBr_3 (see, ref. Tsung-Ying Shen and Charles A. Winter, Adv. Drug Res., 1977, *12*, 176) to give the 5-hydroxy indole, V, which is elaborated, by methods previously

Scheme 5.

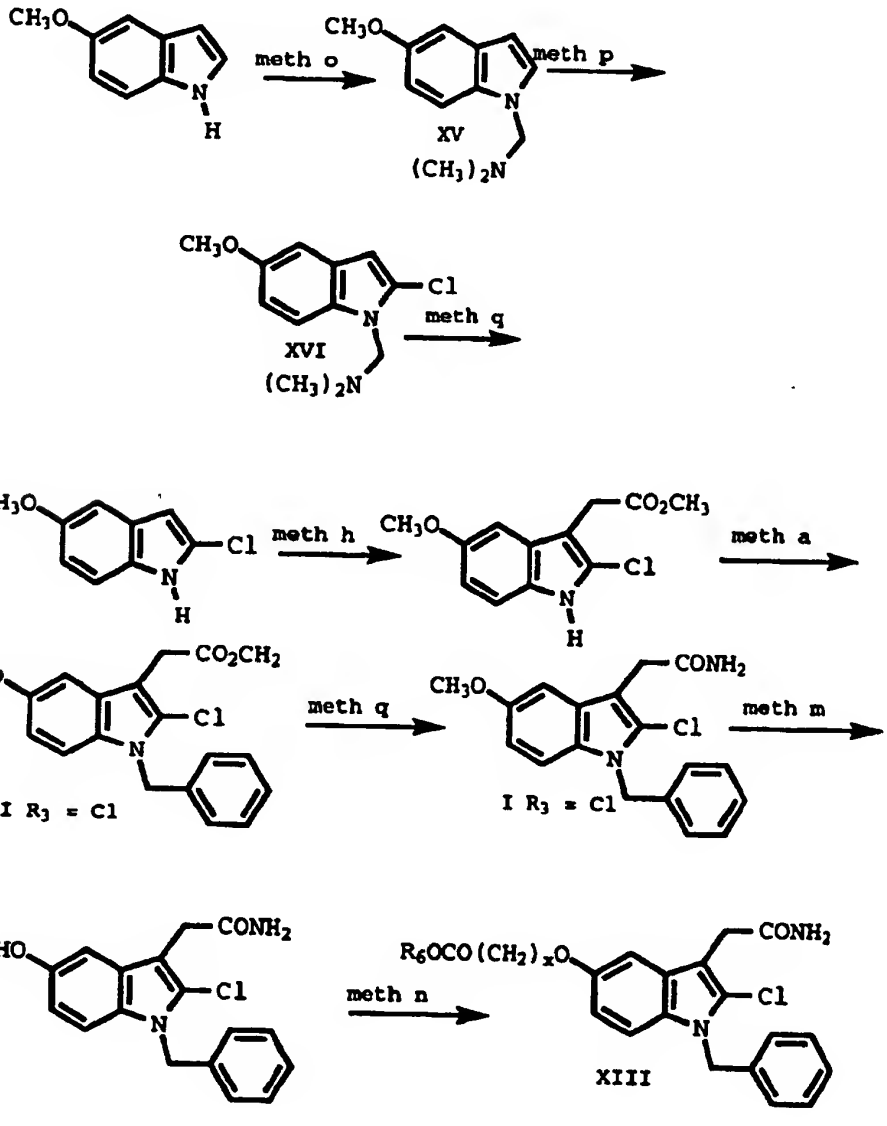


described, to I, where R_1 is hydroxy. 1H-Indole-3-acetamid s, where R_1 is 4- or 5- or 6-m thoxy can be also

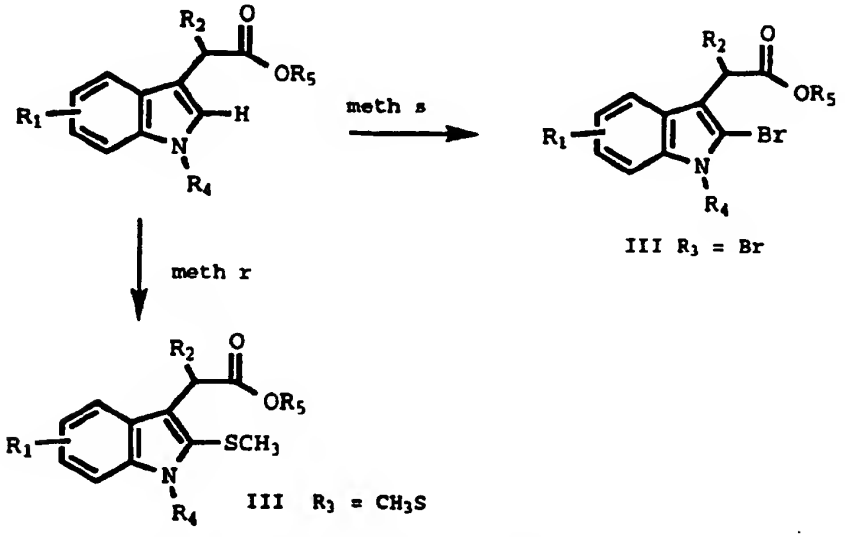
directly demethylated to I (R_1 = hydroxy) by method m. These compounds can then b alkylated to giv compounds of structure XIII. When alkyl acrylates are used, derivatives of XIII are obtained where x is equal to 2. Bromo acetates and 4-bromo-butyrates give esters of structure XIII where x is 1 and 3, respectively. Use of benzyl halide gives the phenylmethyl derivative. All of the compounds where R7 contains an ester group can be converted to their carboxylic acid equivalents, XIV.

The 2-chloro-1H-indole-3-acetamides are best prepared by the reactions outlined in Scheme 6. The 1-dimethylamino substituent on XV is used to direct the lithiation by *sec*-butyl lithium to the 2 position. This on treatment with benzenesulfonyl chloride gives XVI, which on treatment with aqueous HCl, loses the dimethylamino group to give 2-chloro-5-methoxy-1H-indole. Reactions of this indole using methods previously described gives the 2-chloro esters, III. This ester may be converted to the 2-chloro amide, I, using the reagent, $(CH_3)_2AlNH_2$ (method q). These may be O-demethylated and the phenolic intermediate realkylated as described in Scheme 5 to give the compounds of structure XIII, where R_3 is chloro.

Scheme 6.

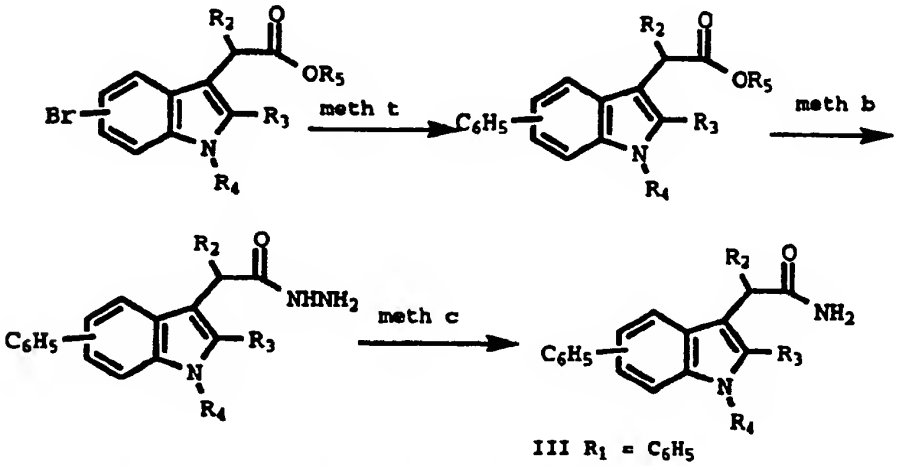


The intermediate 1H-indole-3-aceti acid esters, III, where R_3 is bromo are made by reacting th ester, III, where R_3 is hydrogen, with N-bromosuccinimide (method s). In a similar fashion, methanesulfenyl chloride gives the 3-methylthio indole, III, $R_3 = CH_3S$.

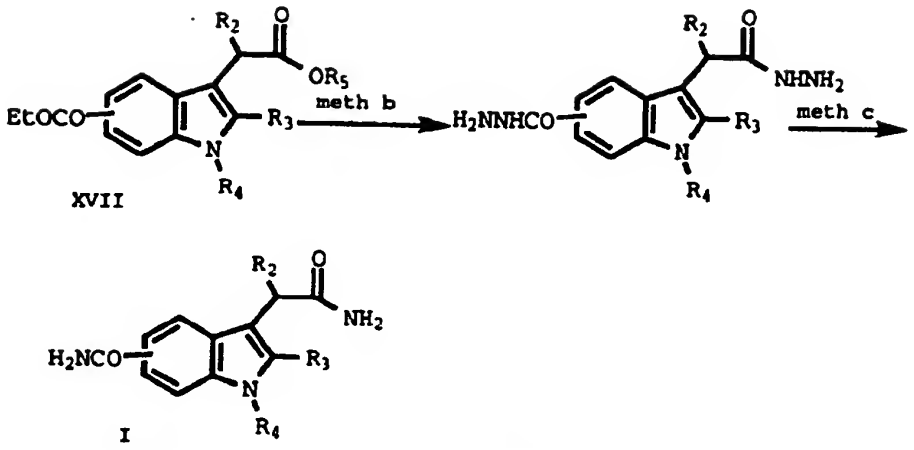


Compounds of structure I where R_1 is phenyl, are made by phenylation (see, ref. N. Miyaura, T. Yamag, A. Suzuk: Snyth. Commun. 1981 11, p. 513-519) of the intermediates where R_1 is Br (method t). This phenylation can be carried

Scheme 7.



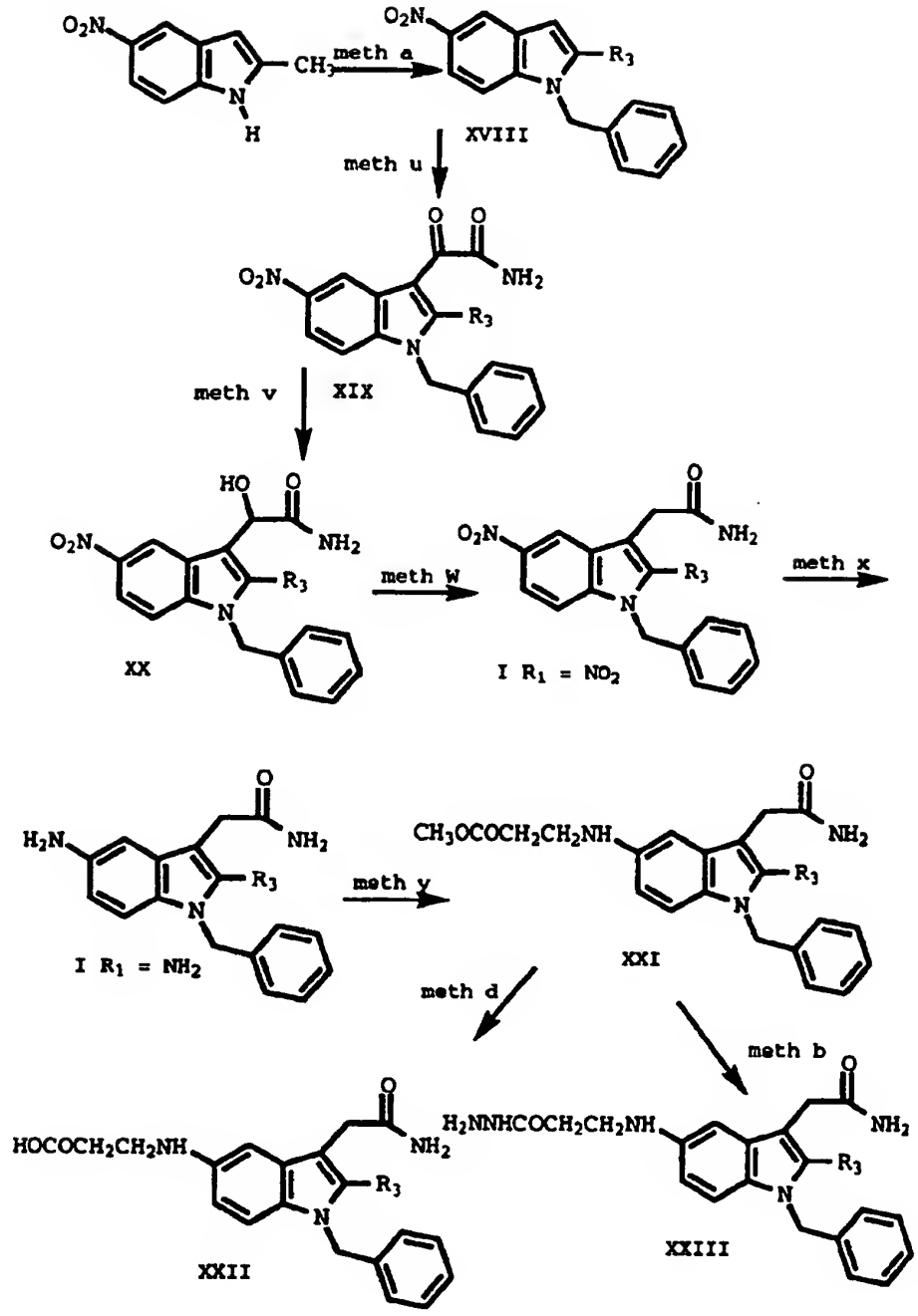
out on any of the appropriate bromo substituted intermediates. The 1H-indole-3-acetamide, I, where R_1 is aminocarbonyl can be made through th appropriate diester. XVII, which is converted by previously described methods to the final diamide, I



The amides, I, where the R_1 substutients contain nitrogen, as well as the compounds where substitution on the amino group contains esters or carboxylic acids, such as XXI and XXII, may be made by the procedures outlined in Scheme 8. 2-Methyl-5-nitro-1H-indole is first benzylated to give the N-substituted derivative, XVIII. Treatment of this indole with oxalyl chloride (method u) followed by the addition of gaseous ammonia gives the oxalamide, XIX. Stepwise reduction of this compound is carried out. The glycolic acid amide, XX, is obtained by treatment of XVIII with $NaBH_4$ (method v). Reduction of this intermediate with triethylsilane (method w) in trifluoroacetic acid results in the acetamide, I, ($R_1 = O_2N$). The nitro function may be reduced catalytically (method x) to give the 5-amino amide (I, $R_1 = NH_2$). Treatment of this amino intermediate with methyl acrylate gives the ester amide XXI (some of the N,N-disubstituted derivative is also obtained in this reaction). This ester may be hydrolyzed with sodium hydroxide to give carboxylic acid amide, XXII. The same ester intermediate, XXI, is reacted with hydrazine to give the hydrazinocarbonyl derivative, XXIII.

6-Methoxy-2-methyl-1H-indole is converted to 6-methoxy-2-methyl-1H-indole-3-actamides by the sequence of reactions outlined in the first 4 steps of Scheme 8.

Scheme 8.



Described below are examples of the present invention which are provided only for illustrative purposes. They are not intended to limit the scope of the present invention in any way as numerous embodiments within the scope of the claims will be apparent to those of ordinary skill in the art.

EXAMPLES

Exampla 1

Preparation of 2.6-Dimethyl-1-(phenylmethyl)-1H-Indole-3-acetamide

A. N-*tert*-Butoxycarbonyl-2, 5-dimethylaniline. A solution of 2,5-dimethylanlline(24.2g, 0.2 mol) and 50.0g(0.229 mol) of di-*tert*-butyl dicarbonate in 200 ml of tetrahydrofuran was heated slowly to reflux and reflux maintained for 2 hours. After cooling, tha reaction mixture was concentrated at reduced pressure and tha residue dissolved in EtOAc. The EtOAc solution was washed with 1N citric acid solution, dried over Na_2SO_4, and concentrated at reduced pressure. Crystallization of the residue from hexane gave 24.0g (54% yield) of N-*tert*-butoxycarbonyl-2,5-dimethylaniline melting at 103-104°C.

Analyses: Calc'd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.32. Found: C, 70.28; H, 8.51; N, 6.60.

B. 2,6-Dimethyl-1H-indole. A solution of 1.3M sec-butyl lithium/cyclohexane (81.0 ml, 0.105 mol) was added slowly to 11.05g (0.05 mol) of N-*tert*-butoxycarbonyl-4-ethoxy-2-methylaniline in 150 ml of THF while keeping the temperature below -40°C with a dry ice-ethanol bath. After 0.25 hours, 7.21g (0.07 mol) of N-methoxy-N-methylacetamide in an equal volume of THF was added dropwise. The reaction mixture was stirred for 1 hour, the cooling bath removed and stirred an additional one hour. It was then poured into a mixture of 500 ml of ether and 500 ml of 1N HCl. The organic layer was separated, washed with water and dried over Na_2SO_4. After removing the solvent there remained 12.5g of crude 1-(2-*tert*-butoxycarbonylamino-4-methylphenyl)-2-propanone. This material and 15 g of trifluoroacetic acid in 250 ml of CH_2Cl_2 was stirred at room temperature for 16 hours. The mixture was washed twice with water, a saturated Na_2CO_3 solution and dried over Na_2SO_4. After removing the solvent, the product was chromatographed on silica eluting with toluene to give 3.2g (44% yield) of 2,6-dimethyl-1H-indole melting at 74-76°C.

Analyses: Calc'd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.47; H, 7.34; N, 9.92.

C. 2,6-Dimethyl-1H-Indole-3-acetic acid methyl ester. To a cooled solution of 2.9g (0.02 mol) of 2,6-dimethyl-1H-indole in 40 ml of THF was added 12.5mL(0.02 mol) of a 1.6M solution of *n*-butyl lithium in hexane keeping the temperature below 10°C with an ice-ethanol bath. After 0.25 hours, 20.0 ml (0.0277 mol) of a 1M solution of $ZnCl_2$ in ether was added. The cooling bath was removed and the mixture stirred for 2 hours, then concentrated at reduced pressure to a wax which was dissolved in 40 ml of toluene. To this solution was added 1.89 ml (0.02 mol) of methyl 2-bromoacetate, the mixture was stirred 24 hours and poured into 100 ml of 1N HCl and 100 ml of EtOAc. The organic layer was washed twice with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica and eluted with 10% EtOAc/toluene to give 3.17g (73%) of 2,6-dimethyl-1H-Indole-3-acetic acid methyl ester as an oil.

Analyses: Calc'd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.61; H, 6.95; N, 6.30.

D. 2,6-Dimethyl-1-(phenylmethyl)-1H-Indole-3-acetic acid methyl ester. Potassium t-butoxide (0.975g, 0.0087 mol) was added to 1.89g (0.0087 mol) of 2,6-dimethyl-1H-indole-3-acetic acid methyl ester in 25 ml of DMF, the mixture was stirred for 0.25 hours, 1.0 ml of benzyl chlorida was added and tha mixture stirred for 72 hours. After diluting with water, tha mixture was extracted with EtOAc, The EtOAc solution was washad four times with water and dried over Na_2SO_4. The solvent was removed at reduced pressure and the residue chromatographed on silica eluting with toluene to give 1.76g (66% yield) of 2,6-dimethyl-1-(phenylmethyl)-1H-indole-3-acetic acid methyl ester as an oil.

Analyses: Calc'd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.18; H, 7.10; N, 4.53.

E. 2,6-Dimethyl-1-(phenylmethyl)-1H-indole-3-acetic acid. A solution of 1.7g (0.0055mol) of 2,6-dimethyl-1-(phenylmethyl)-1H-indole-3-acetic acid methyl ester and 2 ml of 5N NaOH in 50 ml of MeOH was heated to maintain reflux for 3h, diluted with water and made acidic with 5N HCl solution. The mixture was extracted with EtOAc, the EtOAc solution dried over NaSO4 and concentrated at reduced pressure. The residue was crystallized from toluene to give 0.85g (58% yield) of 2,6-dimethyl-1-(phenylmethyl)-1H-indole-3-acetic acid, mp, 179-180°C.

Analyses: Calc'd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 78.01; H, 6.80; N, 4.80.

F.2,6-Dimethyl-1-(phenylmethyl)-1H-indole-3-acetamide.

A solution of 0.48g (1.64 mmol) of 2,6-dimethyl-1-(phanylmethyl)-1H-indole-3-acetic acid in 25 ml of tetrahydrofuran (THF) was cooled with an ice-water bath, 0.45 ml of triethylamina was added followed by 0.13 ml (1.7 mmol) of methyl chloroformat . After 0.5 hour, gaseous NH_3 was bubblad into th reaction mixture for 0.5 hour, the cooling bath removed and tha mixture stirred for 2 hours. It was then poured into water and xtracted with EtOAc, th EtOAc solution washed with a Na_2CO_3 solution, dried(Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from MeOH/water, to give 0.19g (39%

yield) of 2,6-dim thyl-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 160-163°C.

Analyses: Calc'd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.31; H, 6.97; N, 9.31.

Example 2

Preparation of 5-Hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide

A. 5-Methoxy-2-methyl-1H-indole-3-acetic acid methyl ester. A solution of 12.2g (0.0557 mol) of 5-methoxy-2-methyl-1H-indole-3-acetic acid in 150 of MeOH and 1 ml of sulfuric acid was heated to maintain reflux for 15 hours. After cooling, the mixture was diluted with a sodium bicarbonate solution and extracted with EtOAc. The EtOAc solution was washed with a saturated NaCl solution and dried (Na_2SO_4). The solvent was removed at reduced pressure to give 13g of crude 5-methoxy-2-methyl-1H-indole-3-acetic acid methyl ester.

B. 5-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid. The crude 5-methoxy-2-methyl-1H-indole-3-acetic acid methyl ester from A (56 mmol) was dissolved in 250mL of DMF and approximately 10 ml of THF end 2.5g (62 mmol) of 60% NaH/mineral oil added. After 0.5 hour, 8 mL (67 mmol) of benzyl bromide was added and the mixture stirred for 0.75 hours, diluted with water and extracted with EtOAc. The product was chromatographed on silica (20% ether/hexane → 50% ether/hexane) to give 10.1g of a mixture of 5-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic ecid methyl end ethyl esters. This mixture was dissolved in 200 mL of EtOH end 20 mL of 5N NaOH and heated to meintain reflux for 20.75 hours. After cooling the mixture was made acidic with 5N HCl end extracted with EtOAc. The EtOAc solution was washed with NaCl, dried(Na_2SO_4), and concentrated et reduced pressure to give 7.9g (46% yield) of crude 5-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid.

C. 5-Hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid methyl ester. Three mL(30 mmol) of BBr_3 was added to 3.1g(10 mmol) of 5-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid in 250 mL of CH_2Cl_2 end the mixture stirred for 17 hours. After stirring with 1N HCl, some EtOH wes added, the organic layer separated, washed with a saturated NaCl solution, dried and concentrated at reduced pressure to give 2.95g (100% yield) of crude 5-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic ecid. A methanol solution of 1.7g of the material wes treated with sulfuric acid as described in Part A to give efter silice gel chromatography (30% ether/hexane → 60% ether/hexene) 1.5g of 5-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid methyl ester.

D. 5-Hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide. A solution of 750 mg(2.4 mmol) of 5-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid methyl ester and 2 mL of hydrazine in 75 mL of ethanol was heated to maintain reflux for 72 hours. After cooling, 2g of Raney nickel was added cautiously and the mixture heeted at reflux for 4 hours. After cooling, the solvent was decanted off end the solids washed with EtOAc by decanting. The combined solvents where filtered through celite and concentrated at reduced pressure. The residue was crystallized from EtOH to give 570mg (80% yield) of 5-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 185-187°C.

Analyses: Calc'd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.23; H, 6.32; N, 9.69.

Example 3

Preparation of 5-Methoxy-1-(phenylmethyl)-1H-indole-3-acetamide

A. 5-Methoxy-1H-indole-3-acetic acid ethyl ester. As described in Example 1, Part C, 29.44g (0.0.2 mol) of 5-methoxy-1H-indole was treated with 125 mL (0.2 mol) of 1.6M n-butyl lithium in hexane, 200 mL (0.2 mol) of 1M $ZnCl_2$ in ether, and 22.2 mL (0.2 mol) of ethyl 2-bromoacetate to give after chromatography on silica (eluted with 5% EtOAc/toluene) 20g (43% yield) of 5-methoxy-1H-indole-3-acetic acid ethyl ester, as an oil.

Analyses: Calc'd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.01. Found: C, 66.72; H, 6.53; N, 5.91.

B. 5-Methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester. Using the procedure described in Example 1 Part D, 3.15g (0.0135 mol) of 5-methoxy-1H-indole-3-acetic acid ethyl ester was reacted with 1.51g (0.0135 mol) of potassium *t*-butoxide and 1.55mL (0.0135 mol) of benzyl chloride to give after silica chromatography (gradient, toluene → 5% EtOAc/toluene) 3.6g(83%) of 5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester as an oil.

Analyses: Calc'd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 75.53; H, 6.67; N, 4.08.

C. 5-M thoxy-1-(phenylmethyl)-1H-Indole-3-acetic acid hydrazid . A solution of 1.4g (4.33 mmol) of 5-meth xy-1-(phenylmethyl)-1H-ind le-3-acetic acid ethyl ester and 10 mL of hydrazine in 75 mL of EtOH was heated to maintain reflux for 16 hours. On cooling of th reaction mixture a precipitate formed that was filtered to give 1.33g (93% yield) f 5-methoxy-1-(phenylmethyl)-1H-Indole-3-ecetic ecid hydrazide, mp

143-144°C.

Analyses: Calc'd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.91 H, 6.19; N, 13.37.

D. 5-Methoxy-1-(phenylmethyl)-1H-indole-3-acetamide. One gram of Raney nickel was added to 790mg (2.4 mmol) of 5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid hydrazide in 120 mL of EtOH and the mixture heated at reflux for 2 hours. After filtering off the catalyst, the filtrate was concentrated at reduced pressure and the residue triturated with ether to give 675mg (89% yield) of 5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 156-158°C.

Analyses: Calc'd for $C_{18}H_{18}N_2O_2$: C,73.45; H, 6.16; N, 9.52. Found: C, 70.18; H, 5.96; N, 8.93.

Exemple 4

Preparation of 1-Cyclohexylmethyl-5-methoxy-2-methyl-1H-indole-3-acetamide

A. 5-Methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester. Dry hydrogen chloride was bubbled into e solution of 27.95g (0.16 mol) of 4-methoxyphenylhydrazine hydrochloride end 19.72g (0.17 mol) of levuilnic acid in 500 mL of ethanol for 0.5 hours while cooling with an ice-water bath. The bath wes removed end the reaction was slowly heated to reflux and reflux maintained for 20 hours. After cooling the mixture wes poured into water and extracted with EtOAc. The EtOAc solution was washed with e sodium bicarbonate solution and dried over Na_2SO_4. After removing the solvent at reduced pressure, the residue was chromatographed over silica eluting with 5% EtOAc/toluene to give 14.2g (36% yield) of 5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester, mp, 38-40°C.

Analyses: Calc'd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.24 H, 6.88; N, 5.75.

B. 1-Cyclohexylmethyl-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester. Using the procedure described in Example 1 Part D, 4.7g(0.19 mol) of 5-methoxy-1H-indole-3-ecetic acid ethyl ester was reacted with 2.13g (0.019 mol) of potaesium *t*-butoxide end 2.65 mL(0.019 mol) of cyclohexylmethyl bromide to give after silica chromatography (gradient, toluene → 5% EtOAc/toluene) 3.16g(48%) of 1-cyclohexylmethyl-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester as an oil.

Analyses: Calc'd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.66; H, 8.64; N, 4.14.

C. 1-Cyclohexylmethyl-5-methoxy-2-methyl-1H-Indole-3-acetic acid. Using the method described in Example 1, Part E, 3.1g (9.0 mmol) of 1-cyclohexylmethyl-5-methoxy-2-methyl-1H-indole-3-acetic ecid ethyl ester end 5 mL of 5N NaOH were reacted in 50 mL of EtOH to give on workup, 2.1g (74% yield) of 1-cyclohexylmethyl-5-methoxy-2-methyl-1H-indole-3-ecetic acid melting at 173-175°C after crystallization from toluene.

Analyses: Calc'd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.64; H, 8.00; N, 4.52.

D. 1-Cyclohexylmethyl-5-methoxy-2-methyl-1H-indole-3-acetamide. A solution of 0.63g (2.0 mmol) 1-cyclohexylmethyl-5-methoxy-2-methyl-1H-Indole-3-acetic acid and 0.56 mL (4 mmol) of triethylamine in 25 mL of tetrahydrofuran (THF) was reacted with 0.162 mL (2.1 mmol) of methyl chloroformate end then treeted with gaseous NH_3 es described in Example 1, Part F, to give 0.3g (48% yield) of 1-cyclohexylmethyl-5-methoxy-2-methyl-1H-Indole-3-acetamide, mp, 125-126°C.

Analyses: Calc'd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.57; H, 8.35; N, 8.81.

Example 5

Preparation of 5-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide

A. 5-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic ecid ethyl ester. Using the procedure described in Example 1, Part D, 4.07g (0.0165 mol) of 5-methoxy-2-methyl-1H-indole-3-ecetic acid ethyl ester (Exemple 4, Part A) was reacted with 1.85g (0.0165 mol) of potaseium *t*-butoxide end 1.96 mL (0.0165 mol) of benzyl chloride to give efter silica chromatography (gradient, toluene→ 10% EtOAc/toluene) 3.78g (68% yield) of 5-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester, mp, 63-64°C.

Analyses: Calc'd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.76; H, 6.89; N, 4.28.

B. 5-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-ecetic acid hydrazide. A solution of 1.0g (2.98 mmol) of 5-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-ecetic ecid ethyl ester and 5 mL of hydrazine in 50 mL of MeOH was reacted as described in Example 3, Part C, to give by trituration with ether 920 mg (96% yield) of 5-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic ecid hydrazide, mp, 161-162°C.

Analyses: Calc'd for $C_{19}H_{21}N_3O_2$: C, 70.53; H, 8,54; N, 12.99. Found: C, 70.41; H, 6.58; N, 12.93.

C. 5-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide. Using the method es in Example 3, Part D, 945mg (2.9 mmol) of 5-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic ecid hydrazide was reacted in 50 mL of EtOH using 1.5g f Raney nickel. Workup of this reacti n mixture gav a crude product that wae filtered through silica using EtOAc and crystallized from CH_2Cl_2/MeOH to giv 225mg (25 yield)

of 5-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamid , mp, 128-130°C.

Analyses: Calc'd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.00; H, 6.51; N, 9.05.

Example 6

Preparation of 1(2,6-Dichlorophenylmethyl)-5-methoxy-2-methyl-1H-indole-3-ecetamide

A. 1-(2,6-Dichlorophenylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester. A suspension of 80 mg (2 mmol) of 60% NaH/mineral oil was weshed with hexene and placed in 8 mL of DMF. With ice-bath cooling, 494 mg (2 mmol) of 5-methoxy-2-methyl-1H-indole-3-acetic ecid ethyl ester was edded end stirred 1 hour, then 391mg (2 mmol) of alpha,2,6-trichlorotoluene was added and stirring maintained for 1.5 hours. The mixture was diluted with water, extracted with EtOAc, the EtOAc solution washed with water/NaCl, and dried ($MgSO_4$). The solution was concentrated at reduced pressure, and the product chromatographed on silica, eluting with 25% EtOAc/hexane to give 556mg (68% yield) of 1-(2,6-dichlorophenylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester, which solidifled on standing, melting point, 131-133°C.

Analyses: Calc'd for $C_{21}H_{21}Cl_2NO_3$: C, 62.08; H, 5.21; N, 3.45. Found: C, 61.79; H, 5.23; N, 3.51.

B. 1-(2,6-Dichlorophenylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide. Hydrazine (1.3 mL) wes added to 533mg (1.3 mmol) of 1-(2,6-dichlorophenylmethyl)-5-methoxy-2-methyl-1H-indole-3-ecetic acid ethyl ester in 10 mL of EtOH and the mixture heeted to maintain reflux for 6 hours. After cooling the mixture was diluted with water, extracted with EtOAc, the EtOAc solution washed with a sodium chloride solution and dried over $MgSO_4$. The solvent was removed at reduced pressure end the residue crystallized from MeOH to give 250mg (61% yield) of 1-(2,6-dichlorophenylmethyl)-5-methoxy-2- methyl-1H-indole-3-acetic acid hydrazide, mp 194-196°C.

Analyses: Calc'd for $C_{19}H_{19}Cl_2N_3O_2$: C, 58.17; H, 4.88; N, 10.71. Found: C, 58.65; H, 4.98; N, 10.68.

C. 1-(2,6-Dichlorophenylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetamide. Reney nickel was added to 168mg (0.43 mmol) of 1-(2,6-dichlorophenylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide in 10 mL of EtOH and the mixture heated at reflux temperature for 3.5 hours. After cooling, the solvent was decanted from the solids, the solids washed several times with EtOAc and the combined solvents concentrated at reduced pressure. The residue was filtered through silica eluting with EtOAc and then crystallized from MeOH to give 24mg(15% yield) of 1-(2,6-dichlorophenylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetamide, mp, 203-205°C.

Analyses: Calc'd for $C_{19}H_{18}Cl_2N_2O_2$: C, 60.49; H, 4.81; N, 7.42. Found: C, 60.75; H, 4.89; N, 7.65.

Example 7

Preparation of 1-[(4-Benzyloxyphenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetamide

A. 1-[(4-Benzyloxyphenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetic ecid. Using the method described in Example 6, Part A, 2.0g (8.12 mmol) of 5-methoxy-2-methyl-1H-indole-3-ecetic acid ethyl ester, 0.325g (8.12 mmol) of 60% NeH/mineral oil, and 1.88g (8.12 mmol) of 4-benzyloxy-1-chloromethylbenzene were reacted to give on workup 800mg of crude 1-[(4-benzyloxyphenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-ecetic ecid ethyl ester. The crude ester in 50 mL of MeOH end 15 mL of 1N NeOH was heeted et reflux temperature for 3 hours and left standing for 16 hours. After diluting with weter, the mixture was made acidic with 1N HCl and extracted with EtOAc. The EtOAc solution was dried(Ne_2SO_4) and concentrated. The residue was crystallized from MeOH to give 280mg(32% yield) of 1-[(4-benzyloxyphenyl)-methyl)-5-methoxy-2-methyl-1H-indole-3-ecetic ecid, mp, 175-179°C.

Analyses: Calc'd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06 N, 3.37. Found: C, 75.05; H, 6.07; N, 3.47.

B. 1-[(4-Benzyloxyphenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetamide. Using the method in Example 1, F, 170mg(0.41 mmol) of 1-[(4-benzyloxyphenyl)-methyl]-5-methoxy-2-methyl-1H-indole-3-acetic ecid, 0.1 mL of ethyl chloroformate, 1 mL of triethylamine and excess NH_3 were reected to give 60mg (35% yield) of 1-[(4-benzyloxyphenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetamide, after crystallizing from MeOH, melting et 155-157°C.

Analyses: Celc'd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.09; H, 6.35; N, 6.64.

Example 8

Preparati n f 5-Methoxy-2-methyl-1-[(2-pyridyl)methyl]-1H-indole-3-acetamid

A. 5-M thoxy-2-methyl-1-[(2-pyridyl)methyl]-1H-indole-3-acetic acid thyl ester. Using the procedure described in Example 6, Part A, 494mg (2 mmol) f 5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester

was reacted with 160 mg (4 mmol) of 60% NaH/mineral oil and 328mg (2 mmol) of 2-picolyl chloride hydrochloride and after chromatography on silica (eluting with 50% EtOAc/hexana) there was obtained 510mg (75%) of 5-methoxy-2-mathyl-1-[(2-pyridyl)methyl]-1H-indole-3-acetic acid ethyl ester as an oil.

Analyses: Calc'd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.28; H, 6.84; N, 8.44.

B. 5-Methoxy-2-methyl-1-[(2-pyridyl)methyl]-1H-indole-3-acetic acid hydrazide. Using the method described in Exampla 8, Part B, 480mg (1.4 mmol) of 5-methoxy-2-methyl-1-[(2-pyridyl)methyl]-1H-indole-3-acetic acid ethyl ester was reacted with 1.4 mL of hydrazine to give on crystallization from MeOH 304mg(87% yield) of 5-methoxy-2-methyl-1-[(2-pyridyl)methyl]-1H-indole-3-acetic acid hydrazide, mp. 147-148°C.

Analyses: Calc'd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.40; H, 6.21; N, 17.34.

C. 5-Mathoxy-2-methyl-1-[(2-pyridyl)methyl]-1H-indole-3-acetamida.

Using the procedure in Example 6, Part C, 200mg (0.62 mmol) of 5-methoxy-2-mathyl-1-[(2-pyridyl)methyl]-1H-indole-3-acetic acid hydrazide and approximately 1 gram of Raney nickel in 10 mL of EtOH were reacted to give after chromatographing twice on silica eluting with EtOAc followed by 5% MaOH/EtOAc, 54mg (28% yield) of 5-methoxy-2-methyl-1-[(2-pyridyl)methyl]-1H-indole-3-acetamide, as a semi-solid material.

Analyses: Calc'd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 70.04; H, 6.32; N, 13.85.

Exampla 9

Preparation of 2-Ethyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamida

A. N-*tert*-Butoxycarbonyl-4-methoxy-2-methylaniline. By the procedure in Example 1, Part A, 13.7 g(0.1 mole) of 4-methoxy-2-methylaniline was reacted with 25g (0.1145 mol) of di-*tert*-butyl dicarbonate to give 17.25 g (73% yield) of N-*tert*-butoxycarbonyl-4-methoxy-2-methylaniline melting at 80-82°C, after crystallizing from hexane.

Analyses: Calc'd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.86; H, 8.15; N, 5.81.

B. 1-[2-(*tert*-Butoxycarbonylamino)-5-mathoxyphanyl]-2-butanone. A solution of 1.3M sec-butyl lithium/cyclohaxana(81 mL, 0.105 mol) was added slowly to 11.85g (0.05 mol) of N-*tart*-butoxycarbonyl-4-methoxy-2-mathylanilina in 80 mL of THF while keeping the temperature below -40°C with a dry ice-ethanol bath. The bath was removed and the temperature allowed to rise to -20°C and then the bath was replaced. After the temperature had cooled to -60°C, 8.1g (0.052 mol) of N-methoxy-N-methylpropanamide in an equal volume of THF was added dropwise. The reaction mixture was stirred 1 hour, the cooling bath removed and stirred an additional 1 hour. It was then poured into a mixture of 200 mL of ether and 200 mL of 1N HCl. Tha organic layer was saparated, washed with water, dried over Na_2SO_4 and concentrated at reduced pressure to giva 10.9g (74% yiald) of 1-(2-(*tert*-butoxycarbonylamino)-5-methoxyphenyl]-2-butanona, melting at 80-81°C, after chromatography on silica eluting with 5% EtOAc/toluene.

Analyses: Calc'd for $C_{18}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.69; H, 7.89; N, 4.90.

C. 2-Ethyl-5-methoxy-1H-indole. 1-[2-(*tert*-Butoxycarbonylamino)-5-methoxyphenyl]-2-butanone (7.33 g, 0.025 mol) in 120 mL of CH_2Cl_2 and 20 mL of trifluoroacetic acid was stirred for 20h, washed with water, $NaHCO_3$ solution and the product chromatographed on silica (eluted with 20% EtOAc/hexane) to give 2.54g (58% yield) of 2-ethyl-5-methoxy-1H-indole as a white solid, mp 49-50°C.

Anelyses: Calc'd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.64 H, 7.61; N, 8.04.

D. 2-Ethyl-5-methoxy-1H-indole-3-acetic acid methyl ester. As in Example 1, Part C, 3.5g (0.02mole) of 5-mathoxy-2-ethyl-1H-indole was treated with 12.5 mL (0.02 mol) of a 1.6M solution of *n*-butyl lithum in hexane, 20 ml (0.02 mol) of e 1M solution of $ZnCl_2$ in ether, and 1.89mL (0.02 mol) of methyl 2-bromoacetate to give after chromatography on silica (toluene → 10% EtOAc/toluene) 3.32g(59%) of 2-ethyl-5-methoxy-1H-indole-3-acetic acid methyl ester as an oil.

Analyses: Calc'd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.73; H, 6.94; N, 5.39.

E. 2-Ethyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid methyl ester. A solution of 2.47g (0.01 mol) of 2-ethyl-5-methoxy-1H-indole-3-acetic acid methyl ester in 25 mL of DMF was treated with 1.12g (0.01 mol) of potassium *t*-butoxide, stirred 0.5h, and 1.15 mL (0.01 mol) of benzyl chloride added. After 72 hours, the reaction mixture was diluted with water, extracted with EtOAc, the EtOAc solution was washed four times with water and dried over Na_2SO_4. After concentrating at reduced pressure, the product was purified by chromatography n silica, eluting with a gradient, toluene→10% EtOAc/toluene, to give 1.5g (44% yield) of 2-ethyl-5-methoxy-1-(phenylm thyl)-1H-indole-3-acetic acid methyl ester as oil.

Analyses: Calc'd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 75.00; H, 8.99; N, 4.28.

F. 2-Ethyl-5-methoxy-1-(phanylmathyl)-1H-indole-3-acetic acid hydrazide.

Using the method described in Example 3, Part C, 748 mg (2.2 mmol) of 2-ethyl-5-methoxy-1-

(phenylmethyl)-1H-indole-3-acetic acid m thyl ester was reacted with 2.2 mL of hydrazine to give 552mg (74% yield) of 2-athyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-ecetic acid hydrazide, thet crystallized out of the reaction mixture on cooling (melting point, 138-140°C).

Analyses: Calc'd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.13 H, 6.86; N, 12.33.

G. 2-Ethyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide. An ethanol solution of 225mg (0.67 mmol) of 2-ethyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid hydrazide was reacted with approximately 1.5g of Raney nickel as described in Example 6, Part C, and the crude product chromatographed on silica eluting with 50% EtOAc/hexane, EtOAc, and then 5% MeOH/EtOAc to give after crystallizing from MeOH, 46mg (21% yield) of 2-ethyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-ecetamide, mp, 161-166°C.

Analyses: Calc'd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.77 H, 6.94; N, 8.81.

Example 10

Preparation of 5-Methoxy-1-(phenylmethyl)-2-propyl-1H-indole-3-acetamide

A. 1-[2-(*tert*-Butoxycarbonylamino)-5-methoxyphenyl]-2-pentanone. Using the method described in Example 9, Part B, 15.17 g (0.064 mol) of N-*tert*-butoxycarbonyl-4-methoxy-2-methylaniline (Example 9, Part A) was treated with 1.3M sec-butyl lithium/cyclohexane (100 mL, 0.13 mol) end 6.4g (0.064mol) of N-methoxy-N-methylbutanamide to give 14.31g (73% yield) of 1-(*tert*-butoxycarbonylamino-5-methoxyphenyl)-2-pentanone, melting at 77-78°C, after chromatography on silica eluting with 5% EtOAc/toluene.

Analyses: Calc'd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.42; H, 8.09; N, 4.71.

B. 5-methoxy-2-propyl-1H-indole. 1-[2-(*tert*-Butoxycarbonylamino)-5-methoxyphenyl]-2-pentanone (14.27 g, 0.0465 mol) was treated with 20 mL of trifluoroacetic acid ae described in Example 9, Part C and the product crystalized from hexene to give 5.5g (58% yield) of 5-methoxy-2-propyl-1H-indole as a white solid, mp 49-50°C.

Analyses: Calc'd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.36 H, 8.07; N, 7.52.

C. 5-Methoxy-2-propyl-1H-indole-3-acetic acid methyl ester. As in Example 1, Part C, 5.125g (0.0271 mole) of 5-methoxy-2-propyl-1H-indole was treated with 16.9 mL (0.0271 mol) of a 1.6M solution of *n*-butyl lithum in hexane, 27.1 mL (0.0271 mol) of a 1M solution of $ZnCl_2$ in ether, and 2.7mL (0.0271 mol) of methyl 2-bromoacetate to give after chromatography on silica (20% EtOAc/ hexane) 4.65g (66%) of 5-methoxy-2-propyl-1H-indole-3-acetic ecid methyl ester as an oil.

Analyses: Calc'd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.69; H, 7.36; N, 5.63.

D. 5-Methoxy-1-(phenylmethyl)-2-propyl-1H-indole-3-acetic ecid methyl ester. Using the procedure described in Example 1 Part D, 522 mg (2 mmol) of 5-methoxy-2-propyl-1H-indole-3-acetic acid methyl ester was reacted with 80mg (2 mmol) of 60% NaH/mineral oil and 0.24 mL (2 mmol) of benzyl bromide to give after silica chromatography(25% EtOAc/hexane) 501mg (71%) of 5-methoxy-1-(phenylmethyl)-2-propyl-1H-indole-3-acetic acid methyl ester as an oil.

E. 5-Methoxy-1-(phenylmethyl)-2-propyl-1H-indole-3-acetic acid hydrazide. Using the method described in Example 3, Part C, 480 mg (1.37 mmol) of 5-methoxy-1-(phenylmethyl)-2-propy-1H-indole-3-acetic acid methyl ester was reacted with 1.4 mL of hydrazine to give after crystallizing from MeOH 56mg (74% yield) of 5-methoxy-1-(phenylmethyl)-2-propyl-1H-indole-3-ecetic acid hydrazide, mp 140-141°C.

Analyses: Calc'd for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 71.98 H, 7.12; N, 11.98.

F. 5-Methoxy-1-(phenylmethyl)-2-propyl-1H-indole-3-acetamide. An ethanol solution of 160mg (0.46 mmol) of 5-methoxy-1-(phenylmethyl)-2-propyl-1H-indole-3-acetic acid hydrazide was reacted with approximately 1.0g of Raney nickel as described in Example 6, Part C, and the crude product chromatographed on silica eluting with EtOAc to give after crystallizing from MeOH, 55mg (36% yield) of 5-methoxy-1-(phenylmethyl)-2-propyl-1H-indole-3-acetamide, mp, 154-156°C.

Analyses: Calc'd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.05; H, 7.21; N, 8.29.

Example 11

Preparation of 2-Chloro-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide

A. 1-Dimethylaminomethyl-5-methoxy-1H-indole.

A 37% aqueous solution of formaldehyde (11g, 0.176 mol) was added dropwise to 10g (0.068 mol) of 5-methoxy-1H-indole and 17mL (0.176 mol) of 40% aqueous dimethylamine in 100 mL of tetrahydrofuran and the mixture heated to maintain reflux for 3 hours. After cooling water was added and th mixture extracted with EtOAc. The EtOAc solution was washed twice with water, dried (Na_2SO_4), end concentrated at reduced pressure. Th residue was chromatographed on silica eluting with a gradient, CH_2Cl_2 → 2% MeOH/CH_2Cl_2, to give 6.26g (45% yield) of 1-dimethylaminomethyl-5-methoxy-1H-indole as en oil.

Analysas: Calc'd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89; N, 13.71. Found: C, 70.79; H, 7.92; N, 13.64.

B. 2-Chloro-5-methoxy-1H-indole-3-acetic acid methyl ester. Cooling with a dry ice-ethanol bath, 20 mL (0.026 mol) of 1.3M sec-butyl lithium/cyclohexane was added to 5.1g (0.025 mol) of 1-dimethylaminomethyl-5-methoxy-1H-indole in 100 mL of THF keeping the temperature below -50°C. The cooling bath was removed and the temperature allowed to reach 0°C and the bath then replaced. At -60°C, 3.32 mL (0.026 mol) of benzenesulfonyl chloride in 10 mL of THF was added, stirred 0.3 hours, the bath removed, and the temperature allowed to reach 20°C ovar 1 hour. To this mixture was added 100 mL of 1N HCl and 50 mL of EtOAc and the mixture stirred for 20 hours. After making basic with 5N NaOH, the EtOAc layer was separated, washed with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica eluting with toluene to give 1.37g (29% yield) of crude 2-chloro-5-methoxy-1H-indole. To this material (7.55 mmol) in 30 mL of THF was added 4.7 mL (7.55 mmol) of 1.6M n-butyl lithium/hexane keeping the temperature below 10°C with an ethanol-ice bath. After 0.25h, 7.55 mL (7.55 mmol) of 1M $ZnCl_2$/ether was added, stirred 2 hours, concentrated at reduced pressure, and 40 mL of toluene added followed by 0.72 mL (7.55 mmol) of methyl 2-bromoacetate. Tha mixture was stirred for 16 hours, warmed at 76°C for 4h, cooled, and 50 mL of 1N HCl and 40 mL of EtOAc added. After 0.5 hour, the organic layer was separated, dried(Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica and eluted with a solvent gradient (toluene → 20% EtOAc/toluene) to give 0.79g (41% yield) of 2-chloro-5-methoxy-1H-indole-3-acetic acid methyl ester, as an oil.

Analyses: Calc'd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.47; H, 5.19; N, 4.99.

C. 2-Chloro-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide. The method in Example 2, Part B, was used to react 660mg (2.6 mmol) of 2-chloro-5-methoxy-1H-indole-3-acetic acid methyl ester, 140mg (3.5 mmol) of 60% NaH/mineral oil and 0.5 mL of benzyl bromide to give a material that was chromatographed on silica (eluted with 5% ether/hexane → 15% ether/hexane). This crude intermediate, 2-chloro-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid mathyl ester, weighed 710mg (79% yield). One mmol (344mg) of this material was dissolved in 20 mL of benzene, 5 mL of 0.67M $(CH_3)_2AlNH_2$/benzene added, and the mixture heated to maintain reflux for 2 hours, an additional 5 mL of aluminum reagent added and heating continued for 1.5 hours. After cooling with an ice-bath, the mixture was decomposed with 1N HCl, extracted with EtOAc, the EtOAc solution was washed with saturated NaCl, dried (Na_2SO_4), and concentrated at reduced pressure. Chromatography of the residue on silica(eluted with CH_2Cl_2 → 2% MeOH/CH_2Cl_2) gave 50mg of starting material (ester) and 165mg (50% yield) of 2-chloro-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide, mp. 166-168°C.

Analyses: Calc'd for $C_{18}H_{17}ClN_2O_2$: C, 66.07; H, 5.38; Cl, 10.76; N, 8.48. Found: C, 65.75; H, 5.21; Cl, 10.78; N, 8.52.

Example 12

Preparation of 5-Methoxy-2-(methylthio)-1-(phenylmathyl)-1H-indole-3-acetamide

Sulfuryl chloride (0.8 mL, 10 mmol) was added to an ice-bath cooled solution of 1.0 mL of dimethyldisulfide in 25 mL of mathylena chloride, the cooling bath removed, and tha mixture allowed to warm to room temperature. Three mL of this solution (containing mathanasulfenyl chlorida) was added to 320mg (1.1 mmol) of 5-methoxy-1-(phanylmethyl)-1H-indole-3-acetamide (Example 3) in 100 mL of methylena chloride, stirred 0.33 hours, saturated $NaHCO_3$ solution added, stirred well, and the methylene chloride solution separated, washed with saturated NaCl, dried (Na_2SO_4), and concentrated at reduced pressure. The residue chromatographed on silica was eluted with 40% EtOAc/hexane → 100% EtOAc to give 115mg (31% yield) of 5-methoxy-2-(methylthio)-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 195-197°C.

Analyses: Calc'd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.22; S, 9.42. Found: C, 66.57; H, 5.93; N, 7.92; S, 9.88.

Example 13

Preparation of 5-Benzyloxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide

5-Hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide (400mg, 1.4 mmol) was dissolved in 50 mL of DMSO, 40mg (1.0 mmol) of 60% NaH/mineral oil added, stirred approximately 0.5 hour, 0.2 mL of benzyl bromide added and stirring maintained 2.5 hours. Tha mixture was diluted with wat r, extracted with EtOAc, tha EtOAc solution washed with water, saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. The rasidu was chromatographed on silica(eluted with a gradient, CH_2Cl_2 → 2% MeOH/CH_2Cl_2) and crystallized from CH_2Cl_2/MeOH to giv 440mg (82% yield) of 5-benzyloxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 118-120°C.

Analyses: Calc'd for $C_{25}H_{24}N_2O_2$: C, 76.10; H, 6.29; N, 7.29. Found: C, 77.56; H, 6.33; N, 7.16.

Example 14

Preparation of 1-Decyl-5-methoxy-2-methyl-1H-indole-3-acetamide.

A. 1-Decyl-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester. Using the method described in Example 1, Part D, 2.47g (10.0 mmol) of 5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester was reacted with 1.12g (10.0 mmol) of potassium t-butoxide and 2.07 mL (10.0 mmol) of decyl bromide to give after chromatography on silica (eluting with 5% EtOAc/toluene) 2.16g (56% yield) of 1-decyl-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester.

Analysis: Calc'd for $C_{24}H_{37}NO_3$: C, 74.38; H, 9.62; N, 3.61. Found: C, 74.53; H, 9.38; N, 3.57.

B. 1-Decyl-5-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide. A solution of 2.1g (5.4 mmol) of 1-decyl-ethoxy-2-methyl-1H-indole-3-acetic acid ethyl ester and 5 mL of hydrazine in 40 mL of EtOH was heated to maintain reflux for 5 hours, let stand 16 hours, the precipitate filtered and crystallized from MeOH to give 0.65g (32% yield) of 1-decyl-5-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide, mp, 129-131°C.

Analysis: Calc'd for $C_{22}H_{35}N_3O_2$: C, 70.74; H, 9.44; N, 11.25. Found: C, 70.79; H, 9.60; N, 11.13.

C. 1-Decyl-5-methoxy-2-methyl-1H-indole-3-acetamide. Approximately 1.5g of Raney Ni was added to 1.5g (4.0 mmol) of 1-decyl-5-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide in 250 mL of EtOH and the mixture heated at reflux for 3 hours. After cooling the mixture was filtered and the filtrate concentrated at reduced pressure. The residue was crystallized from EtOAc/hexane to give 0.987g (69% yield) of 1-decyl-5-methoxy-2-methyl-1H-indole-3-acetamide, mp, 110-111°C.

Analysis: Calc'd for $C_{22}H_{34}N_2O_2$: C,73.70; H,9.56; N,7.61. Found: C76.80; H,9.36; N,7.95.

Example 15

Preparation of 5-Aminocarbonyl-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide

A. 5-Ethoxycarbonyl-2-methyl-1H-indole-3-acetic acid ethyl ester.

Dry hydrogen chloride was bubbled into a solution of 25g (0.1643 mol) of 4-hydrazinobenzoic acid and 20.5 mL (0.2 mol) of levulinic acid for 0.5 hours and the reaction mixture heated to maintain reflux for 20 hours. After cooling, the mixture was concentrated at reduced pressure, water added, and the mixture extracted with EtOAc/ether. After drying (Na_2SO_4), the solution was concentrated and the residue chromatographed on silica and eluted with a solvent gradient, (toluene → 20% EtOAc/toluene) to give in the later fractions 12g of a mixture of 5-ethoxycarbonyl-2-methyl-1H-indole-3-acetic acid ethyl ester and the intermediate hydrazone. This mixture was treated again with dry HCl in 250 mL of EtOH and heated to maintain reflux for 16 hours. After cooling, the mixture was poured into water and extracted with EtOAc, the EtOAc solution washed with Na_2CO_3 solution and dried (Na_2SO_4). Silica chromatography (toluene → 20% EtOAc/toluene) gave 3.6g (7.6% yield) of 5-ethoxycarbonyl-2-methyl-1H-indole-3-acetic acid ethyl ester, mp, 74-76°C.

Analyses: Calc'd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84 Found: C, 66.54; H, 5.00; N, 10.39.

B. 5-Ethoxycarbonyl-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester.

Using the procedure described in Example 2, Part B, 2.18g (7.5 mmol) of 5-ethoxycarbonyl-2-methyl-1H-indole-3-acetic acid ethyl ester was reacted with 320mg (8 mmol) of 60% NaH/mineral oil and 1.0 mL (8.4 mmol) of benzyl bromide to give after silica chromatography (25%ether/hexane → 50% ether/hexane) 1.6g (56%) of 5-ethoxycarbonyl-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester.

C. 5-Carboxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester.

A solution of 1.6g(4.2 mmol) of 5-ethoxycarbonyl-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester and 4.2 mL of 1N NaOH in 75 mL of EtOH was stirred 2.25 hours, 10 mL of 1N NaOH added, and stirred an additional 18.5 hours. The reaction mixture was acidified with 1N HCl, extracted with EtOAc, the EtOAc solution washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was heated in 150 mL of EtOH for 4.5 hours, and left at room temperature for 96 hours. After concentrating at reduced pressure, the residue was chromatographed on silica (25% ether/hexane → 50% ether/hexane) to give 110mg (7.5% yield) of 5-carboxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester.

D. 5-Hydrazinocarbonyl-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid hydrazid .

Using the method described in Example 3, Part C, 110mg (0.31 mmol) of 5-carboxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester was reacted with 3 mL of hydrazine(total reflux time, 78 hours) to give on cooling of th reaction mixture 40mg (38% yield) of 5-hydrazinocarbonyl-2-methyl-1-(phe-

nylmethyl)-1H-indole-3-acetic acid hydrazide, mp, >255°C.

Analyses: Calc'd for $C_{19}H_{21}N_5O_2$: C, 64.94; H, 6.02; N, 19.93. Found: C, 65.15; H, 6.14; N, 19.62.

E. 5-Aminocarbonyl-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide.

Using the method described in Example 3, Part D, 40mg (0.11 mmol) of 5-hydrazinocarbonyl-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid hydrazide was hydrogenolized using approximately 1g of Raney nickel in 50 mL of EtOH to give after chromatography on silica (gradient, CH_2Cl_2 → 8% MeOH/CH_2Cl_2) 17mg (50% yield) of 5-aminocarbonyl-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide.

Analyses: Calc'd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.07. Found: C, 67.21; H, 5.76; N, 12.66.

Example 16

Preparation of 2-Methyl-5-nitro-1-(phenylmethyl)-1H-indole-3-acetamide.

A. 2-Methyl-5-nitro-1H-indole.

A solution of 17.0g (0.2 mol) of sodium nitrate in 150 mL of sulfuric acid was added dropwise to 26.9g (0.205 mol) of 2-methyl-1H-indole in 150 mL of sulfuric acid keeping the temperature at -10 to 0°C with an ethanol-water bath. After 0.25 hours, the mixture was poured onto ice, extracted with EtOAc, the EtOAc solution washed with water, Na_2CO_3 solution and dried (Na_2SO_4). After concentrating at reduced pressure, the residue was crystallized from EtOH to give 20.86g (59% yield) of 2-methyl-5-nitro-1H-indole, mp, 163-165°C.

Analyses: Calc'd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.36; H, 4.61; N, 16.17.

B. 2-Methyl-5-nitro-1-(phenylmethyl)-1H-indole.

Hexane was used to wash 80mg (2.0 mmol) of 60% NaH/mineral oil and 6 mL of DMF was added followed by 352mg (2.0 mmol) of 2-methyl-5-nitro-1H-indole. After 0.33 hours, 0.24 mL (2.0 mmol) of benzyl bromide was added, stirred 0.5 hours and diluted with water. The mixture was extracted with EtOAc, the EtOAc washed with a saturated NaCl solution, dried ($MgSO_4$) and on concentrating at reduced pressure, crystals formed. These were washed with MeOH to give 400mg (75% yield) of 2-methyl-5-nitro-1-(phenylmethyl)-1H-indole, mp, 150-152°C.

Analyses: Calc'd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.37; H, 5.24; N, 10.53.

C. 2-Methyl-5-nitro-1-(phenylmethyl)-1H-indole-3-glyoxylic acid amide.

To a cooled solution of 380mg (1.4 mmol) of 2-methyl-5-nitro-1-(phenylmethyl)-1H-indole in 10 mL of methylene chloride was added 0.12 mL of oxalyl chloride, the cooling bath was removed and the reaction mixture stirred for 3.0 hours. After concentrating at reduced pressure to a solid, the material was redissolved in 10 mL of methylene chloride and anhydrous ammonia bubbled in for approximately 5 minutes. After concentrating at reduced pressure, the residue was taken up in EtOAc, washed with water, NaCl solution, dried ($MgSO_4$), and concentrated. The residue was crystallized from MeOH to give 315mg (67% yield) of 2-methyl-5-nitro-1-(phenylmethyl)-1H-indole-3-glyoxylic acid amide, mp, 204-206°C.

Analyses: Calc'd for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46. Found: C, 64.32; H, 4.38; N, 12.44.

D. 2-Methyl-5-nitro-1-(phenylmethyl)-1H-indole-3-glycolic acid amide.

To a mixture of 1.04g (3.1 mmol) of 2-methyl-5-nitro-1-(phenylmethyl)-1H-indole-3-glyoxylic acid amide in 30 mL of EtOH was added 148mg (3.9 mmol) of $NaBH_4$, the mixture stirred for 1.0 hour and concentrated at reduced pressure. The residue was stirred with water and EtOAc and the insoluble material filtered to give 1.05mg (100% yield of 2-methyl-5-nitro-1-(phenylmethyl)-1H-indole-3-glycolic acid amide, mp, 120-124°C.

Analyses: Calc'd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 64.88; H, 5.38; N, 12.17.

E. 2-Methyl-5-nitro-1-(phenylmethyl)-1H-indole-3-acetamide.

A solution of 0.927g (2.7 mmol) of 2-methyl-5-nitro-1-(phenylmethyl)-1H-indole-3-glycolic acid amide in 15 mL of trifluoroacetic acid was treated with 1.0 mL (6.0 mmol) of triethylsilene and the mixture stirred for 1.0 hour. After concentrating at reduced pressure, the residue was chromatographed on silica (eluted with EtOAc) and crystallized from MeOH/CH_2Cl_2 to give 455mg (52% yield) of 2-methyl-5-nitro-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 189-192°C.

Analyses: Calc'd for $C_{18}H_{17}N_3O_3$: C, 68.86; H, 5.30; N, 12.99. Found: C, 68.99; H, 5.26; N, 12.95.

Example 17

Preparation f 5-Amino-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamid

A solution of 205mg (0.634 mmol) of 2-methyl-5-nitro-1-(phenylmethyl)-1H-indole-3-acetamide in 30 mL of 2:1 THF/EtOH was hydrogenated at 60 psi (4218 g/cm²) of hydrog n for 4 hours using 0.1g of Pd/C as catalyst. The catalyst was filtered and the filtrate concentrated at reduced pressure. The residue was chromato-

graphed on silica eluting with EtOAc and then 5% MeOH/EtOAc to give 52mg (28% yield) of 5-amino-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 175-178°C.

Analyses: Calc'd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.90; H, 6.57; N, 14.25.

Example 18

Preparation of 2-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]acetic acid ethyl ester.

A. 5-(Carbethoxymethoxy)-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid.

A solution of 590mg (2.0 mmol) of 5-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid (Example 2, Part C) in 30 mL of THF and 10 mL of DMSO was treated with 180mg (4.5 mmol) of 60% NaH/mineral oil and after 10 minutes, 0.25 mL (2.25 mmol) of ethyl 2-bromoacetate was added. The mixture was stirred for 0.5 hour, acidified with 1N HCl and extracted with EtOAc. The EtOAc solution was washed with water, saturated NaCl solution, dried (Na_2SO_4) and concentrated at reduced pressure. After chromatography on silica (eluted with a gradient, $CH_2Cl_2 \rightarrow$ 3% MeOH/CH_2Cl_2) there was obtained 590mg (77% yield) of 5-(carbethoxymethoxy)-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid.

B. 2-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]acetic acid ethyl ester. While cooling at -5°C, 0.16 mL (2.1 mmol) of methyl chloroformate was added to 630mg (1.6 mmol) of 5-(carbethoxymethoxy)-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid and 0.3 mL (2.2 mmol) of triethylamine in 30 mL of CH_2Cl_2 and stirred 10 minutes. Anhydrous ammonia was bubbled into the reaction mixture for 0.5 hour, the mixture washed with water, saturated NaCl solution, dried(Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica and eluted with a gradient($CH_2Cl_2 \rightarrow$ 3% MeOH/CH_2Cl_2) to give after crystallization from ether 270mg (44% yield) of 2-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]acetic acid ethyl ester, mp, 160-161°C.

Analyses: Calc'd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.69; H, 6.38; N, 7.18.

Example 19

Preparation of 2-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]acetic acid.

A solution of 190mg (0.5 mmol) of 2-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]acetic acid ethyl ester and 2 mL of 5N NaOH in 30 mL of EtOH and 10 mL of THF was stirred for approximately 15 hours, the mixture made acidic with 5N HCl and extracted with EtOAc. The EtOAc solution was washed with saturated NaCl solution, dried(Na_2SO_4), and concentrated at reduced pressure. The residue was washed with ether to give 155mg (90% yield) of 2-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]acetic acid, mp, 196-198°C.

Analyses: Calc'd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.35; H, 5.73; N, 7.73.

Example 20

Preparation of 3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]-propanic acid methyl ester.

5-Hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide (550mg, 1.8 mmol), 550mg (4 mmol) of K_2CO_3 and 0.2 mL of methyl acrylate in 40 mL of acetone was heated to maintain reflux for 100 hours (additional methyl acrylate was added at various times). After cooling, the mixture was diluted with water, extracted with EtOAc, the EtOAc solution washed with saturated NaCl solution and dried (Na_2SO_4). After concentrating, the residue was chromatographed on silica (eluted with $CH_2Cl_2 \rightarrow$ 1% MeOH/CH_2Cl_2) and crystallized from CH_2Cl_2-/ether to give 375mg (55% yield) of 3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]-propanic acid methyl ester, mp, 113-115°C.

Analyses: Calc'd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.52; H, 6.38; N, 7.33.

Example 21

3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]-propenic acid.

A. 3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylm thyl)-1H-indol-5-yl]oxy]-propanic acid benzyl ester. Using th procedure described in Example 21, 270mg (0.92 mmol) of 5-hydroxy-2-methyl-1-(ph nylmethyl)-1H-indole-3-acetamide, 0.5g of potassium carbonate and 1 mL of benzyl acrylate in 30 mL of MEK were reacted to giv 130mg f 3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]-propanic acid benzyl ester(chromatographed on silica, eluted with $CH_2Cl_2 \rightarrow$ 7% MeOH/CH_2Cl_2).

B. 3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]-propanic acid. A mixture of 130mg (0.29 mmol) of 3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]-propanic acid benzyl ester and 0.2g of 10% Pd/C was hydrogenated at 40 psi (2812 g/cm^2) of hydrogen for 4.5 hours. The mixture was filterad, and concentrated until the product crystallized. These were washed with ether to give 80mg (75% yield) of 3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]-propanic acid, mp. 201-203°C.

Analyses: Calc'd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 65.88; H, 6.32; N, 6.68.

Example 22

4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid.

A solution of 430mg (1.5 mmol) of 5-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide (Example 2, Part D) in 50 mL of DMSO was treated with 60mg (1.5 mmol) of 60% NaH/mineral oil, and then with 0.26 mL (1.8 mmol) of benzyl bromide. The mixture was stirred 1.5 hours at room temperature, 85°C for 1.5 hours, and room temperature for 16 hours. It was diluted with water, extracted with EtOAc, the EtOAc solution washed with water, saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica (CH_2Cl_2 → 3% MeOH/CH_2Cl_2)to give 315mg (51% yield) of 4-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester. This material was stirred with 1 mL of 5N NaOH in 15 mL of EtOH for 20 hours. The mixture was acidified with 5N HCl, extracted with EtOAc, the EtOAc solution washed with saturated NaCl solution and dried (Na_2SO_4). On concentrating the EtOAc solution, a precipitate formed and was collected to give 245mg (38% yield) of 4-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid, mp. 218-221°C.

Analyses: Calc'd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36 N, 7.36. Found: C, 68.35; H, 6.36; N, 7.00.

Example 23

Preparation of 5-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]pentanoic acid.

As described in Example 23, 125mg (0.43 mmol) of 5-hydroxy-2-methyl-1-(phenylmethyl)-1H-Indole-3-acetamide (Example 2), 30mg of 60% NaH/mineral oil, and 0.1 mL of 5-bromopentanoic acid methyl ester in 15 mL of DMSO were reacted to give 80mg of 5-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]pentanoic acid methyl ester, after chromatography on silica (eluted with CH_2Cl_2 → 2% MeOH/CH_2Cl_2). This material in 5 mL of THF and 15 mL of EtOH was treated with 2 mL of 2N NaOH and the mixture stirred for 18 hours. After acidifying with 5N HCl, the mixture was extracted with EtOAc, the EtOAc solution washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was dissolved in MeOH/CH_2Cl_2, concentrated and diluted with ether to give 80mg (100% yield) of 5-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]pentanoic acid, mp. 168-169°C.

Analyses: Calc'd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 43.53; H, 4.20; N, 4.31.

Example 24

4-[[3-(2-Amino-2-oxoethyl)-2-chloro-1-(phenylmethyl)-1H-Indole-5-yl]oxy]butanoic acid.

A solution of 140mg (0.43 mmol) of 2-chloro-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide (Example 11) in 20 mL of methylene chloride was treated with 2 mL of 1M BBr_3/CH_2Cl_2, stirred for 1.5 hours, stirred with aqueous HCl, the CH_2Cl_2 solvent separated, and washed with water, saturated NaCl solution and dried (Na_2SO_4). On concentrating at reduced pressure, there was obtained 140mg of crude 2-chloro-5-hydroxy-1-(phenylmethyl)-1H-Indole-3-acetamide. This material was dissolved in 15 mL of DMSO, 20 mg of 60% NaH/mineral oil added, and after 5 minutes, 0.1 mL of ethyl 4-bromobutyrate was added. The reaction mixture was heated by oil bath at 70°C for 70 minutes. After cooling, the mixture was diluted with water, extracted with EtOAc, the EtOAc solution washed with water, saturated NaCl solution and dried (Na_2SO_4). After concentrating, a residue was obtained that was chromatographed on silica (eluted with CH_2Cl_2→ 3% MeOH/CH_2Cl_2)to give 105mg of 4-[[3-(2-amino-2-oxoethyl)-2-chloro-1-(phenylmethyl)-1H-indole-5-yl]oxy]butanoic acid ethyl ester. This ester (105mg) was dissolved in 15 mL of EtOH, 1 mL of 5N NaOH added, and the solution stirred for 18 hours. The mixture was made acidic with 5N HCl, and extracted with EtOAc. The EtOAc solution was washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated at reduced pressure. Th residue was dissolved in MeOH/CH_2Cl_2, the solution concentrated, to give 75mg (80% yield) of 4-[[3-(2-amino-2-oxoethyl)-2-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid, mp, 198-200°C.

Analyses: Cal 'd for $C_{21}H_{21}ClN_2O_4$: C, 62.92; H, 5.28; N, 6.99. Found: C, 58.94; H, 4.97; N, 6.41.

Exampl 25

Preparation of 3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]amino]propenoic acid methyl ester.

A solution of 147mg(0.5 mmol) of 5-amino-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide (Example 18) and 2 mL of methyl ecrylete in 5 mL of MeOH was stirred for 65 hours, then concentrated at reduced pressure. The residue was chromatographed on silica and eluted with a gradient (EtOAc → 5% MeOH/EtOAc) to give e major product and e minor product in the leter fractions. The major product was 105mg (55% yield) of 3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]amino]propanoic acid methyl ester.

Analyses: Calc'd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64 N, 11.07. Found: C, 69.87; H, 6.39; N, 11.10.

Example 26

Preparation of 3,3'-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]imino]bis[propanoic acid] dimethyl ester.

From the chromatography of the reaction products obtained in Example 25, the later fractions contained the minor product, 3,3'-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]imino]bis[propenoic acid] dimethyl ester, which, after drying, weighed 52mg.

Example 27

Preparation of 3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]amino]propanoic acid.

One mL of 1N NaOH was added to a solution of 110mg (0.3 mmol) of 3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]amino]propenoic acid methyl ester (Example 26) in 5 mL of MeOH, stirred 1.0 hour, then 1 mL of 1N NaOH was added end the mixture stirred 0.5 hour. Weter was added, then 2 mL of 1N HCl, and the mixture extracted with EtOAc. This was dried ($MgSO_4$) and concentrated at reduced pressure to give 21mg (20% yield) of 3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]amino]propanoic acid.

Example 26

Preparation of 3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]amino]propanoic acid hydrazide.

Hydrazine was edded to 151mg (0.4 mmol) of 3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]amino]propanoic acid methyl ester in 5 mL of MeOH and the mixture heated at reflux for 1.0 hour and stirred at room temperature for 16 hours. After diluting with water, the mixture was extracted with EtOAc, the EtOAc solution washed with saturated NaCl solution, dried ($MgSO_4$) end concentrated at reduced pressure.

Example 29

Preparation of 6-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide.

A. 1-[2-(*tert*-Butoxycarbonylamino)-4-methoxyphenyl]-2-propenone. 12g (87 mmol) of 5-methoxy-2-methylaniline was treated by the method in Example 1, Part A, with 19g (87 mmol)of di-*tert*-butyl dicarbonate to give on concentrating a reaction mixture containing 16.4g (80% yield) of N-*tert*-butoxycarbonyl-5-methoxy-2-methylaniline. This material (69 mmol) was reacted with 106 mL of 1.3M sec-butyl lithium in cyclohexane and then 7.1g (69 mmol) of N-methoxy-N-methylacetamide (as described in Example 9, Part B) to give after chromatography on silica, eluting with 33% EtOAc/hexane, 13.8g (72% yield) of 1-[2-(*tert*-butoxycarbonylamino)-4-methoxyphenyl]-2-propanone.

Analysis: Calc'd for $C_{15}H_{21}N_2O_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 63.80; H, 7.32; N, 5.48.

B. 6-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-glyoxylic acid amide. Using the method in Example 9, Part C, 13.7g 49 mmol) of 1-[2-(*tert*-butoxycarbonylemino)-4-methoxyphenyl]-2-propanone was reacted with 20 mL of trifluoroacetic and the product chromatographed on silica eluting with 20% EtOAc/hexane. There was obtained 4.8g (61% yield) of crude 6-methoxy-2-methyl-1H-indole. By the method in Example 6, Part A, this material (30mmol) was treated with 1.2g (30 mmol) of 60% NaH/mineral oil and 3.6 mL f b nzyl bromide in DMF t give after chromatography on silica (eluting with 25% EtOAc/h xan)4.77g(63% yield) of 6-methoxy-2-methyl-1-(ph nylmethyl)-1H-indole. By th method in Exampl 16, Part C, 1.97g (8 mmol) of 6-methoxy-2-m thyl-1-(phenylmethyl)-1H-indole was reacted with 0.73 mL (8.4 mmol) f oxalyl chloride and then ammonia to give 0.875g (34% yield) of 6-meth xy-2-m thyl-1-(phenylmethyl)-1H-indole-

3-glyoxylic acid amide from EtOAc, mp, 230-234°C.

Analysis: Calc'd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.11; H, 5.71; N, 8.70.

C. 6-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-glycolic acid amide. Using EtOH as a solvent, 4.15g (12.9 mmol) of 6-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-glyoxylic acid amide (Example 16) was reacted with 0.605g (16 mmol) of $NaBH_4$ by the method used in Example 17, Part A, and the crude product was washed with EtOAc and water to give 2.6134g (63%) of 6-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-glycolic acid amide, mp, 196-198°C.

Analysis: Calc'd for $C_{19}H_{20}N_2O_2$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.49; H, 6.23; N, 8.85.

D. 6-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide. Using the method in Example 17, Part B, 720mg (2.2 mmol) of 6-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-glycolic acid amide, 0.4 mL (2.5 mmol) of triethylsilane, and 10 mL of trifluoroacetic acid were reacted and the product chromatographed on silica (eluting with 33% EtOAc/hexane) and crystalized from methylene chloride/MeOH to give 164mg (24% yield) of 6-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 136-139°C.

Analysis: Calc'd for $C_{19}H_{20}N_2O_3$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.72; H, 6.57; N, 9.00.

Example 30

Preparation of 6-Hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide.

To a solution of 1.53g (5 mmol) of 6-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide was added 20 mL (20 mmol) of 1M BBr_3 in methylene chloride and the mixture stirred for 3 hours. Water was added and the mixture extracted with EtOAc. The EtOAc solution was washed with a NaCl solution, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was chromatographed on silica and the product eluted with 5% MeOH/methylene chloride to give 658mg (45% yield) of 6-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 174-179°C.

Analysis: Calc'd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52, Found: C, 72.43; H, 6.08; N, 9.92.

Example 31

Preparation of 4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-6-yl]oxy]butanoic acid ethyl ester.

A solution of 294mg (1 mmol) of 6-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide was treated with 40mg (1 mmol) of 60% NaH/mineral oil and after 1 hours, 0.15 mL (1 mmol) of ethyl 4-bromobutyrate was added. The mixture was stirred for 2 hours, diluted with water and extracted with EtOAc. The EtOAc solution was washed with NaCl solution, dried (MgSO4), and concentrated at reduced pressure. The residue was chromatographed on silica eluting with EtOAc to give (after crystallizing from CH_2Cl_2/MeOH/hexane, 228mg (76% yield) of 4-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-6-yl]oxy]butanoic acid ethyl ester, mp, 126-133°C.

Analysis: Calc'd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.47; H, 6.97; N, 6.80.

Example 32

Preparation of 4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-6-yl]oxy]butanoic acid.

A solution of 100mg (0.245 mmol) of 4-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-6-yl]oxy]butanoic acid ethyl ester and 2 mL of 1N NaOH in 5 mL of EtOH was stirred for 1.5 hours, diluted with water and extracted with EtOAc. The aqueous layer was made acidic to pH 6 with 1N HCl and extracted with EtOAc, the EtOAc dried ($MgSO_4$), and concentrated at reduced pressure. The residue was crystallized from MeOH/CH_2Cl_2 to give 44mg (47% yield) of 4-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-6-yl]oxy]butanoic acid, mp, 180-184°C.

Analysis: Calc'd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.68; H, 6.38; N, 6.37.

Example 33

Preparation of 5-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-6-yl]oxy]pentanoic acid ethyl ester.

Using the procedure in Exampl 33, 147mg (0.5 mmol) of 6-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamid was reacted with 20mg (0.5 mmol) of 60% NaH/mineral oil and 0.08 mL (0.05 mmol) of thyl 5-bromovalerate. After chromatography on silica (eluting first with 50% EtOAc/hexane, then EtOAc) and crystallization from MeOH/CH_2Cl_2 there was obtained 150mg (71% yield) of 5-[[3-(2-amino-2-oxoethyl)-2-methyl-

1-(phenylm thyl)-1H-indol-6-yl] xy]p ntanoic acid thyl est r, mp, 123-135°C.

Analysis: Calc'd for $C_{25}H_{30}N_2O_4$: C, 71.07; H, 7.16; N, 6.63. Found: C, 71.20; H, 7.15; N, 6.73.

Example 34

Preparation of 5-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-6-yl]oxy]pentanoic acid.

As in Example 34, 100mg (0.24 mmol) of 5-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-6-yl]oxy]pentanoic acid ethyl ester was hydrolyzed with 2 mL of 1N NaOH to give after crystallization from $MeOH/CH_2Cl_2$ 53mg (56% yield) of 5-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-6-yl]oxy]pentanoic acid, mp, 103-107°C.

Analysis: Calc'd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.78; H, 6.81; N, 7.34.

Example 35

Preparation of 4-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide.

A. N-*tert*-butoxycarbonyl-3-methoxy-2-methylaniline. By the method in Example 1, Part A, 25.8g (188 mmol) of 3-methoxy-2-methylaniline was treated with 41g (188 mmol)of di-*tert*-butyl dicarbonate to give by chromatography on silica (eluted with 25% EtOAc/hexane) 16.4g (80% yield) of N-*tert*-butoxycarbonyl-3-methoxy-2-methylaniline.

Analysis: Calc'd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 64.31; H, 7.76; N, 6.58.

B. 4-Methoxy-2-methyl-1H-indole.

N-*tert*-Butoxycarbonyl-3-methoxy-2-methylaniline (43g, 0.18 mol) was reacted with 280 mL (0.36 mol) of 1.3M sec-butyl lithium in cyclohexane and then 18.5g (0.18 mol) of N-methoxy-N-methylacetamide as described in Example 9, Part B to give 39.5g of a mixture of 1-[2-(*tert*-butoxycarbonylamino)-6-methoxyphenyl]-2-propanone and starting anilide. This mixture was dissolved in 100 mL of methylene chloride and 40 mL of trifluoroacetic acid end stirred for e total of 26 hours. The mixture was washed with water, dried ($MgSO_4$) end concentrated at reduced pressure. The residue was chromatographed on silica eluting with 20% EtOAc/hexane to give on crystallizetion from CH_2Cl_2/hexene 13.9g of 4-methoxy-2-methyl-1H-indole, mp, 80-86°C.

Analysis: Calc'd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.41; H, 7.08; N, 8.47.

C. 4-Methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester. Using the procedure in Example 1, Part C, 13.9g (86 mmol) of 4-methoxy-2-methyl-1H-indole, 54 mL (86 mmol) of 1.6M n-butyl lithium/hexane, and 86 mL (86 mmol) of 1M $ZnCl_2$/ether were reacted to give after silica chromatography (eluted with 20% EtOAc/hexane) 11.2g (53% yield) of 4-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester, mp, 117-121°C.

Analysis: Calc'd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.29; H, 6.98; N, 5.73.

D. 4-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester. Using the method in Example 16, Part B, 7.4g (30 mmol) of 4-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester, 1.2g (30 mmol) of 60% NaH/mineral oil end 3.6 mL (30 mmol) of benzyl bromide were reacted to give after chromatography on silica and crystallization from MeOH/hexane, 6.16g (61% yield) of 4-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester, mp, 75-80°C.

Analysis: Calc'd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.93; H, 6.66; N, 4.02.

E. 4-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid hydrazide. A solution of 2.8g (8.3 mmol) of 4-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid etyl ester and 10 mL of hydrazine in 40 mL of EtOH was heated to maintain reflux for 16 hours, diluted with water end extracted with EtOAc. The EtOAc solution was washed with NaCl solution, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was crystallized from MeOH to give 2.0g (75% yield) of 4-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid hydrazide, mp, 145-147°C.

Analysis: Calc'd for $C_{19}H_{21}N_3O_2$: C, 70.56; H, 6.55; N, 12.99. Found: C, 70.82; H, 6.87; N, 13.16.

F. 4-Methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide. A mixture of 2.0g (6.2 mmol) of 4-methoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetic acid hydrazide end approximately 1g of Raney Ni were heated at reflux temperature for 1 hour, cooled, methylene chloride added and filtered. The filtrate was concentrated at reduced pressure and the residue chromatographed on silica eluting with 5% MeOH/EtOAc to give 1.5g (79% yield) of 4-meth xy-2-methyl-1-(phenylm thyl)-1H-indole-3-ac tamide, mp, 145-146°C.

Analysis: Calc'd for $C_{19}H_{20}N_2O_2$: C, 74.08; H, 6.54; N, 9.08. Found: C, 75.09; H, 6.48; N, 9.20.

Example 36

Preparation of 4-Hydroxy-2-methyl-1-(phenylmathyl)-1H-indole-3-acetamide.

A solution of 1.45g (4.7 mmol) of 4-mathoxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide and 14.1 mL (14.1 mmol) of 1M BBr_3 in methylena chloride was reacted as described in Example 2, Part C to give after chromatography on silica (eluted with EtOAc/hexane, then EtOAc) 908mg (66% yield) of 4-hydroxy-2-methyl-1- (phanylmethyl) -1H-indole-3-acetamide, mp, 200-208°C.

Analysis: Calc'd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.70; H, 6.420; N, 9.52.

Example 37

Preparation of 4-[[3-(2-Amino-2-oxoethyl)-2-mathyl-1-(phanylmathyl)-1H-indol-4-yl]oxy]butanoic acid athyl ester.

A solution of 294mg (1 mmol) of 4-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamida was treated with 40mg (1 mmol) of 60% NaH/minaral oil and after 1 hour, 0.15 mL (1 mmol) of ethyl 4-bromobutyrate was added. The mixture was stirred for 2 hours, diluted with water and extracted with EtOAc. The EtOAc solution was washed with NaCl solution, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was crystallized from MeOH/hexana to giva a total of 235mg (58% yield) of 4-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]butanoic acid ethyl ester, mp, 115-116°C.

Analysis: Calc'd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.68; H, 6.97; N, 7.02.

Example 38

Preparation of 4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]butanoic acid.

A solution of 100mg (0.245 mmol) of 4-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]butanoic acid ethyl ester and 2 mL of 1N NaOH in 5 mL of EtOH was stirred for 3.0 hours, diluted with water and extractad with EtOAc. The aqueous layer was made acidic to pH 6 with 1N HCl and extracted with EtOAc, the EtOAc dried ($MgSO_4$), and on concantrating at reduced pressure a preciplate formed that was separated and washed with MeOH to giva 40mg (42% yield) of 4-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]butanoic acid, mp, 192-193°C.

Analysis: Calc'd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.38. Found: C, 68.17; H, 6.05; N, 6.99.

Exampla 39

Preparation of 2-[[3-(2-Amino-2-oxoethyl)-2-mathyl-1-(phanylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

Using tha procedure in Exampla 37, 294mg (1 mmol) of 4-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide was treated with 40mg (1 mmol) of 60% NaH/mineral oil and 0.10 mL (1 mmol) of methyl 2-bromoacetate to give, after silica chromatography (eluted with 50%EtOAc/hexane, than EtOAc, followed by 2%MeOH/EtOAc), 278mg (76% yield) of 2-[[3-(2-amino-2-oxoethyl)-2-mathyl-1-(phanylmethyl)-1H-indol-4-yl]oxy]acetic acid mathyl ester, mp, 206-208°C.

Analysis: Calc'd for $C_{24}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 6.65. Found: C, 769.06; H, 5.87; N, 7.40.

Exampla 40

Preparation of 2-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.

A solution of 100mg (0.245 mmol) of 2-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester and 2 mL of 1N NaOH in 5 mL of EtOH was stirred for 2.0 hours, diluted with water and extracted with EtOAc. The aqueous layer was made acidic to pH 6 with 1N HCl and extracted with EtOAc, the EtOAc dried ($MgSO_4$), and concentrated at reduced pressure. The residue was crystallized from MeOH to give 54mg (57% yield) of 2-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid, mp, 225-227°C.

Analysis: Calc'd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.35; H, 5.79; N, 7.94.

Exampl 41

Pr paration of [3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid.

A. [3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosph nic acid dimethyl ester. Using the procedure described in Example 39, 147mg (0.5 mmol) of 5-hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide was reacted with 20mg (0.5 mmol) of 60% NaH/mineral oil and then 80mg (0.0 mmol) of 3-bromopropylphosphonic acid dimethyl ester. The final product was crystallized from MeOH/hexane to give 126mg (57% yield) of [3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester, mp, 136-138°C.

Analysis: Calc'd for $C_{23}H_{29}N_2O_5P$: C, 62.15; H, 6.58; N, 6.30. Found: C, 61.09; H, 6.71; N, 5.94.

B. [3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid. A solution of 100mg (0.23 mmol) of [3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester and 0.24 mL (1.8 mmol) of bromotrimethylsilane in 2 mL of methylene chloride was stirred for 18 hours. The reaction mixture was concentrated at reduced pressure, 5 mL of MeOH added, stirred 0.5 hour, and concentrated. The residue was crystallized from EtOAc/MeCN/HOAc/H_2O to give 40mg (42% yield) of [3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid, mp, 201-203°C.

Analysis: Calc'd for $C_{21}H_{25}N_2O_5P$: C, 60.57; H, 6.05; N, 6.73. Found: C, 60.53; H, 6.08; N, 6.74.

Example 42

Preparation of 2-Bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide.

A. 2-Bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid benzyl ester. N-Bromosuccinimide (450mg, 2.5 mmol) was added to 910mg (2.5 mmol) of 5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid benzyl ester in 75 mL of carbon tetrachloride and the mixture stirred for 0.5 hour. After washing with $Na_2S_2O_3$ solution, water and saturated NaCl solution and drying (Na_2SO_4), the CCl_4 was removed at reduced pressure. The residue was chromatographed on silica (eluted with methylene chloride) and crystallized from ether/hexane to give 765mg (67% yield) of 2-bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid benzyl ester, mp, 89-90°C.

Analysis: Calc'd for $C_{25}H_{22}BrNO_3$: C, 64.66; H, 4.78; N, 3.02. Found: C, 64.43; H, 4.75; N, 2.96.

B. 2-Bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide. A solution of 120mg (0.26 mmol) of 2-bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid benzyl ester and 2 mL of 0.67M $(CH_3)_2AlNH_2$/benzene in 20 mL of benzene was heated for 23.5 hours while adding additional aluminum reagent periodically. The mixture was poured onto ice, decomposed with 1N HCl, and extracted with EtOAc. The extract was washed with saturated NaCl solution, dried (Na_2SO_3) and concentrated at reduced pressure. The residue was chromatographed on silica eluting with a gradient, CH_2Cl_2 → 2%MeOH/CH_2Cl_2, to give 100mg (100% yield) of 2-bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 172-174°C.

Analysis: Calc'd for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.50; Br, 21.41. Found: C, 57.71; H, 4.56; N, 7.42; Br, 21.67.

Example 43

Preparation of 4-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid.

A solution of 600mg (1.6 mmol) of 2-bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide (lot was contaminated with 2,4-dibromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide) and 10 mL of 1M BBr_3/CH_2Cl_2 in 100 mL of CH_2Cl_2 was stirred for 2.5 hours, 100 mL of 1N HCl added, stirred well, and the CH_2Cl_2 layer separated. After washing and drying (Na_2SO_4), the solvent was removed at reduced pressure. The residue was chromatographed on silica and eluted with a gradient (1%MeOH/CH_2Cl_2→ 4%MeOH/CH_2Cl_2) to give in the early fractions 2,4-dibromo-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide (115mg) and in the later fractions 2-bromo-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide (115mg). The material from the later fractions (100mg, 0.28 mmol) was dissolved in 20 mL of DMSO, 20mg of 60% NaH/mineral was added, and after 10 minutes, 0.1 mL of ethyl 4-bromobutyrate was added. After heating for 1.25 hours at 85°C, the mixture was diluted with water, extracted with EtOAc, and the EtOAc solution washed with water, saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica (eluted with 1%MeOH/CH_2Cl_2 → 3%MeOH/CH_2Cl_2) to give 80mg of 4-[[3-(2-amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester as an oil. This material was dissolved in 20 mL of EtOH, 1 mL of 2N NaOH added, and th mixture stirred for 19 hours. After acidifying with 1N HCl, the mixture was extracted with EtOAc, th EtOA solution washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from EtOH/ether to give 80mg of 4-[[3-(2-amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]-butanoic acid.

Analysis: Calc'd for $C_{21}H_{21}BrN_2O_4$: C, 56.64; H, 4.75; N, 6.29. Found: C, 42.71; H, 3.76; N, 4.50.

Example 44

Preparation of 5-Hydroxy-2-(methylthio)-1-(phenylmethyl)-1H-indole-3-acetamide.

A solution of 600mg (1.6 mmol) of 5-methoxy-2-(methylthio)-1-(phenylmethyl)-1H-indole-3-acetamide (Example 12) was reacted with 10 mL of 1M BBr_3/CH_2Cl_2 as described in Example 2, Part C, to give as crude product 440mg (64% yield) of 5-hydroxy-2-(methylthio)-1-(phenylmethyl)-1H-indole-3-acetamide.

Analysis: Calc'd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58; S,9.82. Found: C, 66.45; H, 5.55; N, 8.29; S, 9.72.

Example 45

Preparation of 4-[[3-(2-Amino-2-oxoethyl)-2-(methylthio)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester.

A solution of 465mg (1.4 mmol) of 5-hydroxy-2-(methylthio)-1-(phenylmethyl)-1H-indole-3-acetamide (Example 46), 60mg (1.5 mmol) of 60% NaH/mineral oil and 0.25 mL (1.7 mmol) of ethyl 4-bromoburyrate was reacted as in Example 45. After washing the crude product with EtOH/ether, there was obtained 510mg (83% yield) of 4-[[3-(2-amino-2-oxoethyl)-2-(methylthio)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester, mp, 109-111°C.

Analysis: Calc'd for $C_{24}H_{28}N_2O_4S$: C, 65.43; H, 6.41; N, .36; S, 7.28. Found: C, 65.24; H, 6.44; N, 6.12; S, 7.30.

Example 46

Preparation of 4-[[3-(2-Amino-2-oxoethyl)-2-(methylthio)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid.

As described in Example 45, 245mg (0.58 mmol) of 4-[[3-(2-amino-2-oxoethyl)-2-(methylthio)-1-(phenylmethyl)-1H-indol-5-yl]oxy] butanoic acid ethyl ester (Example 47) was hydrolyzed with 1 mL of 5N NaOH in 5 mL of THF and 15 mL of EtOH. The crude product was washed with EtOH/ether to give 195mg (85% yield of 4-[[3-(2-amino-2-oxoethyl)-2-(methylthio)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid, mp, 187-188°C.

Analysis: Calc'd for $C_{22}H_{24}N_2O_4S$: C, 64.05; H, 5.86; N, 6.79; S, 7.77. Found: C, 63.81; H, 5.89; N, 6.80; S, 7.66.

Example 47

Preparation of 5-(4-Amino-4-oxobutoxy)-2-(methylthio)-1-(phenylmethyl)-1H-indole-3-acetamide.

Ten mL of 0.6M $(CH_3)_2AlNH_2$/benzene was added to 200mg (0.45 mmol) of 4-[[3-(2-amino-2-oxoethyl)-2-methylthio-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester (Example 46) in 25 mL of benzene and the mixture heated at 50°C for 1.75 hours. After cooling the mixture was decomposed with ice and 1N HCl added, The mixture was extracted with EtOAc, the EtOAc solution washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from EtOH/CH_2Cl_2 to give 155mg (84% yield) of 5-(4-amino-4-oxobutoxy)-2-(methylthio)-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 185°C.

Analysis: Calc'd for $C_{22}H_{25}N_3O_3S$: C, 64.21; H, 6.12; N, 10.21; S, 7.79. Found: C, 64.42; H, 6.54; N, 8.97; S, 7.11.

Example 48

Preparation of 5-Methoxy-2-methyl-1-tetradecyl-1H-indole-3-acetamide.

A. 5-Methoxy-2-methyl-1-tetradecyl-1H-indole-3-acetic acid ethyl ester. Using the method described in Example 8, Part A, 2.0g (8.12 mmol) of 5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester was reacted with 0.325g of 80% NaH/mineral oil and 1.84g (8.1 mmol) of tetradecyl bromide to give after chromatography on silica (eluting with 15% EtOAc/hexane) 1.66g (46% yield) of 5-methoxy-2-methyl-1-tetradecyl-1H-indole-3-acetic acid ethyl ester.

Analysis: Calc'd for $C_{28}H_{45}NO_3$: C, 75.80; H, 10.22; N, 3.16. Found: C, 75.93; H, 10.32; N, 3.28.

B. 5-Methoxy-2-methyl-1-tetradecyl-1H-indole-3-acetic acid. A soluti n of 1.60g (3.6 mmol) of 5-methoxy-2-methyl-1-tetrad cyl-1H-indole-3-acetic acid thyl ester and 10 mL f 1N NaOH in 25 mL of MeOH was stirred 16 hours, made acidic with 1N HCl, and the precipitate filtered to give 1.36g (90% yield) f 5-methoxy-2-methyl-1-tetradecyl-1H-indole-3-acetic acid, mp, 105-107°C.

Analysis: Calc'd for $C_{26}H_{41}NO_3$: C, 75.40; H, 9.94; N, 3.37. Found: C, 76.96; H, 10.37; N, 3.57.

C. 5-Methoxy-2-methyl-1-t tradecyl-1H-indole-3-acetamid . Oxalyl chloride (1 mL) was added t 1.36g (3.2 mmol) of 5-methoxy-2-methyl-1-tetradecyl-1H-indole-3-acetic acid in 50 mL of methylene chloride and 1 drop of DMF and after stirring for 1 hour, the reaction mixture was concentrated at reduced pressure. The residue was dissolved in 50 mL of THF and anhydrous ammonia bubbled in for 0.5 hour. After diluting with EtOAc, the mixture was washed with water, dried (Na_2SO_4), and concentrated. the residue was chromatographed on silica and eluted with 2% MeOH/methylene chloride to give 0.42g (32% yield) of 5-methoxy-2-methyl-1-tetradecyl-1H-indole-3-acetamide, mp, 117-118°C.

Analysis: Calc'd for $C_{26}H_{42}N_2O_3$: C, 75.32; H, 10.21; N, 6.76. Found: C, 74.41; H, 9.87; N, 7.67.

Example 49

Preparation of 4-[[2-Amino-2-oxoethyl)-2-methyl-1-tetradecyl-1H-indol-5-yl]oxy]butanoic acid.

A. 5-Hydroxy-2-methyl-1-tetradecyl-1H-indole-3-acetamide. A solution of 300mg (0.75 mmol) of 5-methoxy-2-methyl-1-tetradecyl-1H-indole-3-acetamide (Example 14, Part C) in 30 mL of methylene chloride was treated with 2 mL of 1N BBr_3/CH_2Cl_2 and the mixture stirred for 3 hours. The mixture was poured into water and 100 mL of EtOAc and the organic layer separated, washed with Na_2CO_3 solution, dried (Na_2SO_4) and concentrated at reduced pressure to give approximately 300mg of crude 5-hydroxy-2-methyl-1-tetradecyl-1H-indole-3-acetamide.

Analysis: Calc'd for $C_{25}H_{40}N_2O_2$: C, 74.96; H, 10.06; N, 6.99. Found: C, 74.51; H, 9.55; N, 8.31.

B. 4-[[2-Amino-2-oxoethyl)-2-methyl-1-tetradecyl-1H-indol-5-yl]oxy]butanoic acid ethyl ester.
5-Hydroxy-2-methyl-1-tetradecyl-1H-indole-3-acetamide. (300mg, 0.75 mmol) was dissolved in 10 mL of DMF, 40mg (1.0 mmol) of 60% NaH/mineral oil added, and the mixture stirred for 0.5 hour. Thereafter, 0.143 mL (1.0 mmol) of ethyl 4-bromobutyrate was added, the mixture stirred for 20 hours., diluted with water and extracted with EtOAc. The EtOAc solution was washed 4 times with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from EtOH/water to give 0.12mg (31% yield) of 4-[[2-amino-2-oxoethyl)-2-methyl-1-tetradecyl-1H-indol-5-yl]oxy]-butanoic acid ethyl ester, mp, 77-78°C.

Analysis: Calc'd for $C_{31}H_{50}N_2O_4$: C, 72.34; H, 9.79; N, 5.44. Found: C, 72.13; H, 9.63; N, 5.17.

C. 4-[[2-Amino-2-oxoethyl)-2-methyl-1-tetradecyl-1H-indol-5-yl]oxy]butanoic acid. A solution of 120mg (0.233 mmol) of 4-[[2-amino-2-oxoethyl)-2-methyl-1-tetradecyl-1H-indol-5-yl]oxy]butanoic acid ethyl ester and 1 mL of 5N NaOH in 20 mL of MeOH was heated to maintain reflux for 1 hour, cooled and poured into 100 mL of water and made acidic with 5N HCl. The mixture was extracted with EtOAc, the EtOAc solution dried (Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from MeOH to give 50mg (44% yield) of 4-[[2-amino-2-oxoethyl)-2-methyl-1-tetradecyl-1H-indol-5-yl]oxy]butanoic acid, mp, 159-161°C.

Analysis: Calc'd for $C_{29}H_{46}N_2O_4$: C, 71.57; H, 9.53; N, 5.76. Found: C, 71.44; H, 9.39; N, 5.70.

Example 50

Preparation of [4-[[3-(2-Amino-2-oxoethyl)-1-hexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid.

A. 1-Hexyl-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester. 5-Methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester was dissolved in 25 mL of DMF end 0.3g(7.5 mmol) of 60% NaH/mineral oil was edded. After 0.25 hours, 1.1 mL(7.5 mmol) of hexyl iodide was added and the mixture stirred for 16 hours. The mixture was diluted with water, extracted with ethyl acetate and the ethyl acetate solution washed with water. After drying (Na_2SO_4), the solution was concentrated at reduced pressure and the residue chromatographed on silica gel(eluted with 5% EtOAc/toluene) to give 1.01g(61% yield) of 1-hexyl-5-methoxy-2-methyl-1H-indole-3-acetic acid ethvl ester.

Analysis for $C_{20}H_{29}NO_3$:			
Calculated	C, 74.75;	H, 5.96;	N, 4.36.
Found	C, 70.31;	H, 6.68;	N, 3.93.

B. 1-Hexyl-5-methoxy-2-methyl-1H-indole-3-acetamide.
A 2M solution of Al(CH3)3/toluene (15 mL, 0.03 mol) was added to 1.61g (0.03 mol) of ammonium chlorid while slowly keeping the temperature at 5-7°C with an ice-water bath. The bath was removed, the mixture stirred for 0.5 hour and 1.01g (3.05 mmol) of 1-h xyl-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl

ester was edded. After stirring for 18 hours, 10 mL of water was edded cautiously and the mixture added to 1N HCl and a large volume of ethyl acetate. The organic layer was separated, washed with water, sodium bicarbonate solution and dried (Na_2SO_4). After removing the solvent at reduced pressure the residue was crystallized from MeOH/water to give 0.37g (40% yield) of 1-hexyl-5-methoxy-2-methyl-1H-indole-3-acetamide, mp. 120-121°C.

Analysis for $C_{18}H_{26}N_2O_2$:			
Calculated	C, 71.49;	H, 8.67;	N, 9.26.
Found	C, 71.64;	H, 8.54;	N, 9.21.

C. 1-Hexyl-5-hydroxy-2-methyl-1H-indole-3-acetamide.
A mixture of 1 mL of 1M BBr_3/methylene chloride and 0.24g (0.79 mmol) of 1-hexyl-5-methoxy-2 -methyl-1H-indole-3 -acetamide in 20 mL of methylene chloride as stirred for 16 hours, diluted with ethyl acetate and washed twice with water. The solution was dried (Na_2SO_4) and the solvent removed al reduced pressure to give 0.23g of crude 1-hexyl-5-hydroxy-2-methyl-1H-indole-3-acetamide.
D. [4-[[3-(2-Amino-2-oxoethyl)-1-hexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester.
1-Hexyl-5-hydroxy-2-methyl-1H-indole-3-acetamide (230mg, 0.8 mmol) was dissolved in 10 mL of DMF and 26mg (0.8 mmol) of 60% NaH/mineral oil edded. The mixture wee stirred for 1 hour, 0.115 mL (0.8 mmol) of ethyl 4-bromobutyrate edded end stirring continued for 96 hours. The mixture was diluted with water, extracted with ethyl acetate, the ethyl acetate washed with water and dried (Na_2SO_4). The solution was concentrated at reduced pressure and the residue chromatographed on silica gel (eluted with 3% MeOH/methylene chloride) to give 170mg (53% yield of [4-[[3-(2-amino-2-oxoethyl)-1-hexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester, mp, 69-71°C.

Analysis for $C_{23}H_{34}N_2O_4$:			
Calculated	C, 68.63;	H, 8.51;	N, 6.96.
Found	C, 68.90;	H, 8.59;	N, 6.80.

E. [4-[[3-(2-Amino-2-oxoethyl)-1-hexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid.
A mixture of 170mg(0.42 mmol) of [4-[[3-(2-amino-2-oxoethyl)-1-hexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester and 1 mL of 5N NaOH in 20 mL of MeOH was heated to maintain reflux for 2.5 hours, cooled, poured into water and made strongly acidic with 5N HCl. The mixture was extracted with ethyl acetate, dried (Na_2SO_4), concentrated at reduced pressure and the residue crystallized from MeOH. There was obtained 37mg(24% yield) of [4-[[3-(2-amino-2-oxoethyl)-1-hexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid. mp, 169-170°C.

Analysis for $C_{21}H_{30}N_2O_4$:			
Calculated	C, 67.35;	H, 8.07;	N, 7.48.
Found	C, 67.59;	H, 8.06	N, 7.42.

Example 51

5-Methoxy-2-methyl-1-octyl-1H-indole-3-acetamide.
A. 5-Methoxy-2-methyl-1-octyl-1H-indole-3-acetic acid ethyl ester.
Using the procedure described in Example 50, Part A, 2.47g(0.01 mol) of 5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester was reacted with 0.48g (0.012 mol) of 60% NaH/mineral oil and then 2.17 mL(0.012 mol) of iodooctane. The product was chromatographed on silica gel and eluted with 5% EtOAc/toluene to give 1.85g(51% yield) of 5-methoxy-2-methyl-1-octyl-1H-indole-3-acetic acid ethyl ester as an oil.

Analysis for $C_{22}H_{33}NO_3$:

Calculated	C, 73.50; H, 9.25; N, 3.90.
Found	C, 73.47; H, 9.33; N, 3.83.

B. 5-Methoxy-2-methyl-1-octyl-1H-indole-3-acetic acid hydrazide.
A mixture of 1.8g(5 mmol) of 5-methoxy-2-methyl-1-octyl-1H-indole-3-acetic acid ethyl and 3 mL of hydrazine in 125 mL of ethanol was heated to meintain reflux for 16 hours. The mixture was poured into water, extracted with ethyl acetate, washed with water and dried (Na_2SO_4). After removing the solvent at reduced pressure the residue was crystallized from EtOH/water to give 1.29g(75% yield) of 5-methoxy-2-methyl-1-octyl-1H-indole-3-acetic acid hydrazide, mp, 135-136°C.

Analysis for $C_{20}H_{31}N_3O_2$:			
Calcualted	C, 69.53;	H, 9.04;	N, 12.16.
Found	C, 69.69;	H, 9.07;	N, 11.89.

C. 5-Methoxy-2-methyl-1-octyl-1H-indole-3-acetamide.
A mixture of 1.27g (3.68 mmol) of 5-methoxy-2-methyl-1-octyl-1H-indole-3-acetic acid hydrazide and 1g of Raney Ni in 60 mL of ethanol was heated to maintain reflux for 3 hours, cooled, the solvent poured off the settled catalyst, treated with filter aid and filtered. The filtrate was concentrated to give 1.03g (85% yield) of 5-methoxy-2-methyl-1-octyl-1H-indole-3-acetamide, mp, 96-98°C.

Analysis for $C_{20}H_{30}N_2O_2$:			
Calculated	C, 72.69;	H, 9.15;	N, 8.48.
Found	C, 72.48;	H, 9.26;	N, 8.33.

Example 52

Preparation of [4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-octyl-H-indol-5-yl]oxy]butanoic acid.

A. 5-Hydroxy-2-methyl-1-octyl-1H-indole-3-acetamide.
A solution of 1.03g (3.1 mmol) of 5-methoxy-2-methyl-1-octyl-1H-indole-3-acetamide and 5 mL of 1M BBr_3/methylene chloride in 50 mL of methylene chloride was stirred for 24 hours, poured into water and 150 mL of ethyl acetate added. The organic layer was separated, washed with $NaHCO_3$ solution, dried(Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel by eluting with 5% MeOH/methylene chloride to give 316mg (32% yield) of 5-hydroxy-2-methyl-1-octyl-1H-indole-3-acetamide.

B. [4-[[3-(2-Amino-2-oxoethyl)-2-methyl-octyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester.
5-Hydroxy-2-methyl-1-octyl-1H-indole-3-acetamide (316mg, 1.0 mmol) was reacted with 240mg (1.0 mmol) of 60% NaH/mineral and then 0.143 mL(1 mmol)of ethyl 4-bromobutyrate as described in Example 50, Part D. The product was chromatographed on silica gel (eluted with 3% MeOH/methylene chloride) to give 230mg (53% yield) of [4-[[3-(2-amino-2-oxoethyl)-2-methyl-octyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester, mp, 80-85°C.

Analysis for $C_{26}H_{38}N_2O_4$			
Calculated	C, 69.74;	H, 8.90;	N, 6.51.
Found	C, 67.56;	H, 9.01;	N, 5.95.

C. [4-[[3-(2-Amino-2-oxoethyl)-2-methyl-octyl-1-H-indol-5-yl]oxy]butanoic acid.
Using the method of Exemple 1, Part E, 230mg (0,53 mmol) of [4-[[3-(2-amino-2-oxoethyl)-2-methyl-octyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester was hydrolyzed with 2 mL of 5N NaOH to give after crystallization from MeOH, 97mg (45% yield) f [4-[[3-(2-amino-2-oxoethyl)-2-methyl-octyl-1-H-indol-5-yl]oxy]butanoic acid, mp, 164-165°C.

Analysis for $C_{23}H_{34}N_2O_4$:			
Calculated	C, 68.63;	H, 8.51;	N, 6.96.
Found	C, 66.40;	H, 8.30;	N, 6.82.

Example 53

Preparation of [4-[[3-(2-Amino-2-oxoethyl)-1-decyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid.

A. 1-Decyl-5-hydroxy-2-methyl-1H-indole-3-acetamide. A mixture of 5 mL of 1 M BBr_3/methylene chloride and 0.98g(2.73 mmol) of 1-decyl-5-methoxy-2-methyl-1H-indole-3-acetamide in 40 mL of methylene chloride was reacted as described in Example 50, Part C to give 0.81g(60% yield) of crude 1-decyl-5-hydroxy-2-methyl-1H-indole-3-acetamide.

B. [4-[[3-(2-Amino-2-oxoethyl)-1-decyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester.
1-Decyl-5-hydroxy-2-methyl-1H-indole-3-acetamide (810mg, 3.35 mmol) was reacted with 96mg (2.4 mmol) of 60% NaH/mineral oil and then 0.32 mL (2.4 mmol) of ethyl 4-bromobutyrate as described in Example 50, Part D to give a product that was chromatographed on silica gel (eluted with 3% MeOH/methylene chloride) to give 590mg (55% yield) of [4-[[3-(2-amino-2-oxoethyl)-1-decyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester, mp, 93-95°C.

Analysis for $C_{27}H_{42}N_2O_4$:			
Calculated	C, 70.71;	H, 9.23;	N, 6.11.
Found	C, 70.57;	H, 9.03;	N, 6.17.

C. [4-[[3-(2-Amino-2-oxoethyl)-1-decyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid.
A mixture of 590mg (1.3 mmol) of [4-[[3-(2-amino-2-oxoethyl)-1-decyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester and 1.5 mL of 5N NaOH in 20 mL of MeOH was heated to maintain reflux for 2.5 hours, cooled, poured into water and made strongly acidic with 5N HCl. The precipitate was filtered and recrystallized from MeOH. There was obtained 430mg (77% yield) of [4-[[3-(2-amino-2-oxoethyl)-1-decyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid, mp, 163-165°C.

Analysis for $C_{25}H_{38}N_2O_4$:			
Calculated	C, 69.74;	H, 8.90;	N, 6.51.
Found	C, 70.63;	H, 8.83;	N, 6.98.

Example 54

Preparation of [4-[[3-(2-Amino-2-oxoethyl)-1-cyclohexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid.

A. 1-Cyclohexyl-5-hydroxy-2-methyl-1H-indole-3-acetamide. A mixture of 2 mL of 1M BBr_3/methylene chloride and 330mg (1.05 mmol) of 1-cyclohexyl-5-methoxy-2-methyl-1H-indole-3-acetamide in 25 mL of methylene chloride was reacted as described in Example 50, Part C to give 300mg of crude 1-cyclohexyl-5-hydroxy-2-methyl-1H-indole-3-acetamide.

Analysis for $C_{18}H_{24}N_2O_2$:

Calculated	C, 71.97; H, 8.05; N, 9.33.
Found	C, 69.14; H, 7.60; N, 8.69.

B. [4-[[3-(2-Amino-2-oxoethyl)-cyclohexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid thyl ester.
1-Cyclohexyl-5-hydroxy-2-methyl-1H-indole-3-acetamide (300mg, 1.0 mmol) was reacted with 40mg (1.0 mmol) f 60% NaH/mineral oil and then 0.143 mL(1.0 mmol) of ethyl 4-bromobutyrate as described in Example 50, Part D to give a product that was chromatographed on silica gel (eluted with 2%

MeOH/m thyl ne chloride) to give 190mg (46% yield) of [4-[[3-(2-amino-2-oxoethyl)-1-cyclohexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester, mp, 92-94°C.

Analysis for $C_{24}H_{34}N_2O_4$:			
Calculated	C, 69.54;	H, 8.27;	N, 6.76.
Found	C, 69.72;	H, 8.33;	N, 6.70.

C. [4-[[3-(2-Amino-2-oxoethyl)-1-cyclohexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid.
A mixture of 190mg (0.46 mmol) of [4-[[3-(2-amino-2-oxoethyl)-1-decyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester and 2 mL of 5N NaOH in 20 mL of MeOH was heated to maintain reflux for 2.5 hours, cooled, poured into water and made strongly acidic with 5N HCl. The precipitate was filtered and recrystallized from MeOH. There was obtained 50mg (28% yield) of [4-[[3-(2-amino-2-oxoethyl)-1-cyclohexyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid. mp, 212-214°C.

Analysis for $C_{22}H_{30}N_2O_4$:

Calculated C, 68.37; H, 7.82; N, 7.25.

Found C, 68.19; H, 7.54; N, 7.02.

Example 55

Preparation of [3-[[3-(2-Amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-5-yl]oxy]propyl]phosphonic acid.

A. 1-([1,1'-Biphenyl]-2-ylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester.
5-Methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester (988mg, 4 mmol) was added to 160mg (4 mmol) of NaH/mineral oil (previously washed with hexane), the mixture stirred for 0.5 hours end 0.74 mL (4 mmol) of 2-(bromomethyl)biphenyl added. After 2 hours, water was added and the mixture extracted with ethyl ecetate. The ethyl ecetate was washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The residue wes chromatographed on silica gel eluting with 20% EtOAc/hexane to give 1.18g (72% yield) of 1-([1,1'-biphenyl]-2-ylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester as an oil.

B. 1-([1,1'-Biphenyl]-2-ylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetamide.
A mixture of 1.18g(2.86 mmol) of l-([1,1'-biphenyl]-2-ylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester and 3 mL of hydrazine in 20 mL of ethanol was heated to maintain reflux for 16 hours. After cooling, water was added and the mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried($MgSO_4$), and concentrated to give 1.02g of 1-([1,1'-biphenyl]-2-ylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide. A mixture of 576mg (1.44 mmol) of this material and 300mg of Raney Ni in 20 mL of ethanol was heated to maintain reflux for 3 hours. After cooling the solvent was decanted and the Raney Ni washed twice with methylene chloride. The combined organic solvents were concentracted at reduced pressure and the residue chromatographed on silica gel and eluted with ethyl acetate to give 369mg (67% yield) of 1-([1,1'-biphenyl]-2-ylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetamide.

C. 1-([1,1'-Biphenyl]-2-ylmethyl)-5-hydroxy-2-methyl-1H-indole-3-acetamide.
A solution of 369mg (0.96 mmol) of 1-([1,1'-biphenyl]-2-ylmethyl)-5-methoxy-2-methyl-1H-indole-3-acetamide and 4 mL of 1M BBr_3/methylene chloride in 20 mL of methylene chloride was stirred for 6 hours. The mixture was concentrated et reduced pressure, the residue dissolved in ethyl ecetate, washed with water, brine and dried ($MgSO_4$). After concentrating at reduced pressure, the residue was chromatographed on silica gel and eluted with EtOAc to give 295mg (85% yield) of 1-([1,1'-biphenyl]-2-ylmethyl)-5-hydroxy-2-methyl-1H-indole-3-acetamide.

D. [3-[[3-(2-Amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.
1-([1,1'-Biphenyl]-2-ylmethyl)-5-hydroxy-2-methyl-1H-indole-3-acetamide (295mg, 0.8 mmol) was edded to 32mg (0.8 mmol) of NaH/mineral oil in 10 mL of DMF, stirred 1 hour, 121mg (0.8 mmol) of (3-bromopropyl)phosphonic acid dimethyl ester added and stirring maintained for 5.5 hours. The mixture was diluted with water, extracted with ethyl acetate, the ethyl acetate washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel eluting with a gradient, EtOAc→10%MeOH/EtOAc to giv 140mg (34% yield) of [3-[[3-(2-amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

E. [3-[[3-(2-Amino-2-oxoethyl)-1-([1,1-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-5-yl]oxy]propyl]phos-

phonic acid.

[3-[[3-(2-Amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (130mg, 0.25 mmol) and 0.3 mL (3 mmol) of trimethylsilyl bromide in 2 mL of methylene chloride was stirred for 16 hours, 5 mL of MeOH added, stirred 0.75 hours and concentrated at reduced pressure. The residue was crystallized from EtOAc/MeCN/HOAc/water to give 41mg (33% yield) of [3-[[3-(2-amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-5-yl]oxy]propyl]phosphonic acid, mp, 200-202°C.

Analysis for $C_{27}H_{29}N_2O_5P$:			
Calculated	C, 65.84;	H, 5.94;	N, 5.69.
Found	C, 65.56;	H, 5.85;	N, 5.74.

Example 56

Preparation of 2-Ethyl-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.

2-Ethyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide (5.05g, 15.7 mmol) and 47 mL of 1M BBr_3 in 100 mL of methylene chloride was reacted as described in Example 56, Part C to give a product that was chromatographed on silica gel eluting with EtOAc to give 3.64g (75% yield) of 2-ethyl-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide as a yellow foam.

Analysis for $C_{19}H_{20}N_2O_2$:			
Calculated	C, 74.00;	H, 6.54;	N, 9.08.
Found	C, 73.55;	H, 6.40;	N, 8.73.

Example 57

Preparation of [4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1-H-indol-5-yl]oxy]butanoic acid ethyl ester.

2-Ethyl-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide (308mg,1 mmol) was reacted with 40mg (1 mmol) of 60% NaH/mineral oil and then with 0.15 mL (1 mmol) of ethyl 4-bromobutyrate as described in Example 56, Part D to give a product that was chromatographed on silica gel eluting with 50% EtOAc/hexane to give 231mg (55% yield) of [4-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1-H-indol-5-yl]oxy]butanoic acid ethyl ester.

Analysis for $C_{25}H_{30}N_2O_4$:			
Calculated	C, 71.07;	H, 7.16;	N, 6.63.
Found	C, 71.21;	H, 7.24;	N, 6.53.

Example 58

Preparation of [4-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1-H-indol-5-yl]oxy]butanoic acid.

A mixture of 200mg (0.5 mmol) of [4-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1-H-indol-5-yl]oxy]butanoic acid ethyl ester and 4 mL of 1N NaOH in 10 mL of EtOH was stirred for 1.5 hours, diluted with water and extracted with EtOAc. The aqueous layer was made acidic to pH 5 with 1N HCl, extracted with EtOAc, the EtOAc solution washed with brine and dried ($MgSO_4$). The solvent was evaporated at reduced pressure, the residue stirred with ether/MeOH and the insoluble material filtered to give 120mg (61% yield) of [4-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1-H-indol-5-yl]oxy]butanoic acid, mp, 196-199°C.

Analysis for $C_{23}H_{26}N_2O_4$:			
Calculated	C, 70.03;	H, 6.64;	N, 7.10.
Found	C, 69.96;	H, 6.78;	N, 6.85.

Example 59

Preparation of 2-Ethyl-5-(4-hydrazino-4-oxobutoxy)-1-(phenylmethyl)-1H-indole-3-acetamide.

A mixture of 211mg (0.05 mmol) of [4-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1-H-indol-5-yl]oxy]butanoic acid ethyl ester and 1 mL of hydrazine in 5 mL of ethanol was heated to maintain reflux for 5 hours. The mixture was diluted with water, extracted with ethyl acetate, the ethyl acetate washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was stirred with MeOH and the insoluble material filtered to give 177mg (87% yield) of 2-ethyl-5-(4-hydrazino-4-oxobutoxy)-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 176-179°C.

Analysis for $C_{23}H_{28}N_4O_3$:			
Calculated	C, 67.63;	H, 6.91;	N, 13.72.
Found	C, 67.58;	H, 7.01;	N, 13.95.

Example 60

Preparation of 5-(4-Amino-4-oxobutoxy)-2-ethyl-1-(phenylmethyl)-1H-indole-3-acetamide.

A mixture of 150mg (0.37 mmol) of 2-ethyl-5-(4-hydrazino-4-oxobutoxy)-1-(phenylmethyl)-1H-indole-3-acetamide and 200mg of Raney Ni in 15 mL of ethanol was heated to maintain reflux for 2 hours. After cooling, the EtOH was poured off and the Raney Ni washed twice with methylene chloride. The combined washes were filtered, concentrated at reduced pressure and the residue chromatographed on silica eluting with EtOAc, then 10% MeOH/EtOAc to give 69mg (47% yield) of 5-(4-amino-4-oxobutoxy)-2-ethyl-1-(phenylmethyl)-1H-indole-3-acetamide, mp 176-179°C.

Analysis for $C_{23}H_{27}N_3O_3$:			
Calculated	C, 70.20;	H, 6.92;	N, 10.68.
Found	C, 69.92;	H, 7.13;	N, 10.64.

Example 61

Preparation of [3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

5-Hydroxy-2-ethyl-1-(phenylmethyl)-1H-indole-3-acetamide (308mg, 1.0 mmol) was added to 40mg(1.0 mmol) of NaH/mineral oil (washed with hexanes) in 4 mL of DMF, stirred 0.5 hours, 196mg (0.85 mmol) of (3-bromopropyl)phosphonic acid dimethyl ester added and stirring maintained for 6.5 hours. The mixture was diluted with water, extracted with ethyl acetate, the ethyl acetate washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel eluting with EtOAc, 5% MeOH/EtOAc, then 10% MeOH/EtOAc to give 289mg (59% yield) of [3-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

Analysis for $C_{24}H_{31}N_2O_5P$:			
Calculated	C, 62.89;	H, 6.82;	N, 8.11.
Found	C, 62.72;	H, 6.97;	N, 6.29.

Exampl 62

Preparation of [3-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid.

[3-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (150mg, 0.33 mmol) and 0.35 mL (2.6 mmol) of trimethylsilyl bromide in 2 mL of methylene chloride was stirred for 18 hours, 5 mL of MeOH added, stirred 1.0 hour and concentrated at reduced pressure. The residue was crystallized from EtOAc/MeCN/HOAc/water to give 138mg (97% yield) of [3-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid, mp, 194-196°C.

Analysis for $C_{22}H_{27}N_2O_5P$:			
Calculated	C, 61.39;	H, 6.32;	N, 6.51.
Found	C, 61.35;	H, 6.38;	N, 6.35.

Example 63

Preparation of [3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid monomethyl ester.

A mixture of 162mg (0.35 mmol) of [3-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester and 5 mL of 1N NaOH in 10 mL of MeOH was heated to maintain reflux for 5 hours, diluted with water and extracted with ethyl acetate. The aqueous layer was made acidic to pH 2-3 with 1N HCl and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure to give 120mg (77% yield) of [3-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid monomethyl ester.

Analysis for $C_{23}H_{29}N_2O_5P$:			
Calculated	C, 62.15;	H, 6.58;	N, 6.30.
Found	C, 63.15;	H, 6.45;	N, 4.81.

Example 64

Preparation of [3-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-5-yl]oxy]propyl]phosphonic acid.

A. 1-[(3-Chlorophenyl)methyl]-2-ethyl-5-methoxy-1H-indole-3-acetic acid ethyl ester.

2-Ethyl-5-methoxy-1H-indole-3-acetic acid ethyl ester (1.82g, 7.4 mmol) was added to 296mg (7.4 mmol) of NaH/mineral oil (previously washed with hexane), the mixture stirred for 0.5 hours and 0.93 mL (7.4 mmol) of 3-chlorobenzyl chloride added. After 21 hours, water was added and the mixture extracted with ethyl acetate. The ethyl acetate was washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 20% EtOAc/hexane to give 2.13g (75% yield) of 1-[(3-chlorophenyl)methyl]-2-ethyl-5-methoxy-1H-indole-3-acetic acid ethyl ester as an oil.

Analysis for $C_{22}H_{24}ClNO_3$:			
Calculated	C, 68.48;	H, 6.27;	N, 6.63.
Found	C, 68.25;	H, 6.52;	N, 3.45.

B. 1-[(3-Chlorophenyl)methyl]-2-ethyl-5-methoxy-1H-indole-3-acetic acid hydrazide.

A mixture of 1.93g (5 mmol) of 1-[(3-chlorophenyl)methyl]-2-ethyl-5-methoxy-1H-indole-3-acetic acid ethyl ester and 5 mL of hydrazine in 20 mL of ethanol was heated to maintain reflux for 19 hours. After cooling, water was added and the mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), and concentrated to give 1.144g (62% yield) of 1-[(3-chlorophenyl)methyl]-2-ethyl-5-methoxy-1H-indole-3-acetic acid hydrazide.

Analysis for $C_{20}H_{22}ClN_3O_2$:			
Calculated	C, 64.60;	H, 5.96;	N, 11.30.
Found	C, 64.37;	H, 6.13;	N, 11.18.

C. 1-[(3-Chlorophenyl)methyl]-2-ethyl-5-methoxy-1H-indole-3-acetamide.

A mixture of 340mg (0.92 mmol) of 1-[(3-chlorophenyl)methyl]-2-ethyl-5-methoxy-1H-indole-3-acetic acid hydrazide and 200mg of Raney Ni in 20 mL of ethanol was heated to maintain reflux for 2.5 hours. After cooling the solvent was decanted and the Raney Ni washed twice with methylene chloride. The combined organic solvents were filtered, concentrated at reduced pressure and the residue chromatographed on silica gel eluting with ethyl acetate to give 244mg (74% yield) of 1-[(3-chlorophenyl)methyl]-2-ethyl-5-methoxy-1H-indole-3-acetamide.

D. 1-[(3-Chlorophenyl)methyl]-2-ethyl-5-hydroxy-1H-indole-3-acetamide.

A solution of 226mg (0.63 mmol) of 1-[(3-chlorophenyl)methyl]-2-ethyl-5-methoxy-1H-indole-3-acetamide and 2.5 mL of 1M BBr_3/methylene chloride in 15 mL of methylene chloride was stirred for 6 hours. The mixture was concentrated at reduced pressure, the residue dissolved in ethyl acetate, washed with water, brine and dried($MgSO_4$). After concentrating at reduced pressure, the residue was chromatographed on silica gel and eluted with EtOAc to give 174mg (81% yield) of 1-[(3-chlorophenyl)methyl]-2-ethyl-5-hydroxy-1H-indole-3-acetamide.

E. [3-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

1-[(3-Chlorophenyl)methyl]-2-ethyl-5-hydroxy-1H-indole-3-acetamide (170mg, 0.5 mmol) was added to 20mg (0.5 mmol) of NaH/mineral oil in 10 mL of DMF, stirred 1 hour, 121mg (0.8 mmol) of (3-bromopropyl)phosphonic acid dimethyl ester added and stirring maintained for 4 hours. The mixture was diluted with water, extracted with ethyl acetate, the ethyl acetate washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel eluting with EtOAc then 10%MeOH/EtOAc to give 99mg (40% yield) of [3-[[3-(2-amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-5-yl]oxy]propyl] phosphonic acid dimethyl ester.

F. [3-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]propyl]phosphonic acid.

[[3-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (99mg, 0.2 mmol) and 0.21 mL (1.6 mmol) of trimethylsilyl bromide in 2 mL of methylene chloride was stirred for 16 hours, 5 mL of MeOH added, stirred 0.75 hours and concentrated at reduced pressure. The residue was crystallized from EtOAc/MeCN/HOAc/water to give 60mg(65% yield) of [3-[[3-(2-amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-5-yl]oxy]propyl]phosphonic acid, mp, 203-205°C.

Analysis for $C_{22}H_{26}ClN_2O_3O_5P$:			
Calculated	C, 56.84;	H, 5.64;	N, 6.03.
Found	C, 56.80;	H, 5.68;	N, 5.96.

Example 65

Preparation of 4-(2-Hydrazino-2-oxoethoxy)-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide.

A mixture of 484mg (1.3 mmol) of 2-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester (Example 39) and 2 mL of hydrazine in 10 mL of ethanol was heated to maintain reflux for 16 hours, 10 mL of ethanol added, heated an additional 4 hours and cooled. Ethyl acetate and water were added and the insoluble material filtered: The ethyl acetate solution was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was combined with the precipitate above to give 435mg (91% yield) of 4-(2-hydrazino-2-oxoethoxy)-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 207-210°C.

Analysis for $C_{20}H_{22}N_4O_3$:			
Calculated	C, 65.56;	H, 6.05;	N, 15.29.
Found	C, 65.57;	H, 6.14;	N, 15.40.

Example 66

Preparation of 4-(2-Amino-2-oxoethoxy)-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide.

A mixture of 230mg (0.63 mmol) of 4-(2-hydrazino-2-oxoethoxy)-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide and 300mg of Raney Ni in 40 mL of ethanol was heated to maintain reflux for 4 hours. The mixture was cooled. the EtOH poured off the catalyst, and the catalyst washed twice with methylene chloride. The combined solvents were filtered, concentrated and the residue chromatographed on silica gel and on eluting with 10% MeOH/EtOAc, 25mg (11% yield) of 4-(2-amino-2-oxoethoxy)-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide were obtained. This material melted at 190-207°C.

Analysis for $C_{20}H_{21}N_3O_3$:			
Calculated	C, 68.36;	H, 6.02;	N, 11.96.
Found	C, 68.08;	H, 6.55;	N, 13.28.

Example 67

Preparation of [[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]methyl]phosphonic acid diethyl ester.

4-Hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide (294mg, 1 mmol) was added to 40mg (1 mmol) of 60% NaH/mineral oil (previously washed with hexane) in 2 mL of DMF, stirred 0.33 hours, 1.1g (4 mmol) of iodomethylphosphonic acid diethyl ester added, stirred 72 hours, 1.1g (4 mmol) of iodomethylphosphonic acid diethyl ester added and stirring continued 24 hours. The mixture was diluted with water, extracted with ethyl acetate, the ethyl acetate washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate, then 10% MeOH/EtOAc to give 206mg (46% yield) of [[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]methyl]phosphonic acid diethyl ester.

Example 68

Preparation of [[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]methyl]phosphonic acid.

[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]methyl]phosphonic acid diethyl ester (206mg, 0.46 mmol) and 0.49 mL (3.7 mmol) of trimethylsilyl bromide in 2 mL of methylene chloride was stirred for 16 hours, 5 mL of MeOH added, stirred 1.0 hour and concentrated at reduced pressure. The residue was crystallized from EtOAc/MeCN/HOAc/water to give 52mg (29% yield) of [[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]methyl]phosphonic acid, mp, 195-198°C.

Analysis for $C_{19}H_{21}ClN_2O_5P$:			
Calculated	C, 58.76;	H, 5.45;	N, 7.21.
Found	C, 58.52;	H, 5.32;	N, 7.26.

Example 69

Preparation of 1-[(3-Chlorophenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetamide.

A. 1-[(3-Chlorophenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ster. Using th procedure described in Exampl 65, Part A. 741mg (3 mmol) of 5-methoxy-2-methyl-1H-indole-3-acetic acid

ethyl ester (Example 35, Part C) was reected with 120mg (3 mmol) of 60% NeH/mineral il and th n 0.38 mL (3 mmol) of 3-chlorobenzyl chloride to give a product that chrometographed on silica gel (eluted with 20% EtOAc/hexane) to give 790mg(70% yield) of 1-[(3-chlorophenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester, mp, 113-115°C.

Analysis for $C_{21}H_{22}ClNO_3$:

Calculated	C, 67.83; H, 5.96; N, 3.77.
Found	C, 70.39; H, 6.31; N, 3.82.

B. 1-[(3-Chlorophenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide.
A mixture of 780mg(2 mmol) of 1-[(3-chlorophenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester and 2 mL of hydrazine in 10 mL of ethanol was heated to maintain reflux for 16 hours, poured into ethyl acetate/water and the ethyl ecetate separated, weshed with brine and dried ($MgSO_4$).
After concentrating, the residue was stirred with MeOH end the insoluble materiel filtered to give 698mg (98% yield) of 1-[(3-chlorophenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide, mp, 160-162°C.

Analysis for $C_{19}H_{20}ClN_3O_2$:			
Calculated	C, 63.77;	H, 5.63;	N, 11.74.
Found	C, 63.97;	H, 5.70;	N, 11.56.

C. 1-[(3-Chlorophenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetamide.
A mixture of 675mg (1.9 mmol) of 1-[(3-chlorophenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide and 500mg of Raney Ni in 25 mL of ethanol wes heated to maintain reflux for 3.5 hours and cooled to room temperature. The ethanol wes decanted and the Raney Ni washed twice with methylene chloride. The combined solventa were filtered, concentrated at reduced pressure and the residue chromatographed on silica gel (eluted with EtOAc) to give 503mg (77% yield) of 1-[(3-chlorophenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetamide, mp, 171-173°C.

Analysis for $C_{19}H_{19}ClN_2O_2$:			
Calculated	C, 66.57;	H, 5.59;	N, 8.17.
Found	C, 66.79;	H, 5.73;	N, 8.17.

Example 70

Preparation of 1-[(3-Chlorophenyl)methyl]-5-hydroxy-2-methyl-1H-indole-3-acetamide.

A solution of 483mg (1.4 mmol) of 1-[(3-chlorophenyl) methyl]-5-methoxy-2-methyl-1H-indole-3-acetamide and 5.6 mL of 1M BBr_3/methylene chloride in 20 mL of methylene chloride was stirred for 5 hours, 2 mL of 1M BBr_3/methylene chloride added and stirred 16 hours. The mixture was poured into water, extracted with ethyl acetate, the ethyl acetate solution washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted using a gradient, 50% EtOAc/hexane→EtOAc, to give 155mg of starting material, 1-[(3-chlorophenyl)methyl]-5-methoxy-2-methyl-1H-indole-3-acetamide, end 220mg (48% yield) of 1-[(3-chlorophenyl)methyl]-5-hydroxy-2-methyl-1H-indole-3-ecetamide, mp, 173-177°C.

Analysis for $C_{18}H_{17}ClN_2O_2$:			
Calculated	C, 65.75;	H, 5.21;	N, 8.52.
Found	C, 65.93;	H, 5.32;	N, 8.48.

Example 71

Preparation of [[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid ethyl ester.

1-[(3-Chlorophenyl)methyl]-4-hydroxy-2-methyl-1H-indole-3 acetamide (206mg, 0.63 mmol) was added to 25mg (0.63 mmol) of 60% NaH/mimeral oil(previously washed with hexane) in 6 mL of DMF, stirred 0.5 hours, 0.06 mL(0.63 mmol) of methyl 2-bromoacetate added and stirred 2.5 hours. The mixture was diluted with water, extracted with ethyl acetate, the ethyl acetate washed with brine, dried (MgS_4) and concentrated at reduced pressure. The residue was stirred with MeOH and the insoluble material filtered to give 184mg (73% yield) of [[3-(2-amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid ethyl ester, mp, 180-183°C.

Analysis for $C_{21}H_{21}ClN_2O_4$:			
Calculated	C, 62.92;	H, 5.28;	N, 6.99.
Found	C, 63.06;	H, 5.29;	N, 6.93.

Example 72

Preparation of [[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]methyl]acetic acid sodium salt.

A mixture of 155mg (0.39 mmol) of [[3-(2-amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid ethyl ester and 4 mL of 1N NaOH in 10 mL of ethanol was heated 0.5 hours, allowed to cool and the precipitate filtered to give 140mg (88% yield) of [[3-(2-amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]acetic acid sodium salt, mp, >250°C.

Analysis for $C_{20}H_{18}ClN_2O_4Na$:			
Calculated	C, 58.76;	H, 4.44;	N, 6.85.
Found	C, 59.01;	H, 4.55;	N, 6.75.

Example 73

Preparation of [[3-(2-Amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid sodium salt.

A. 1-([1,1'-Biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester.

5-Methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester (1g, 4 mmol) was added to 160mg (4 mmol) of NaH/mineral oil (previously washed with hexane), the mixture stirred for 1.0 hours and 0.13 mL (4 mmol) of 2-(bromomethyl)biphenyl added. After 3 hours, water was added and the mixture extracted with ethyl acetate. The ethyl acetate was washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting wtih 20% EtOAc/hexane to give 1.18g (71% yield) of 1-([1,1'-biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester as an oil.

B. 1-([1,1'-Biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide. A mixture of 1.18g (2.9 mmol) of 1-([1,1'-biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1H-indole-3-acetic acid ethyl ester and 3 mL of hydrazine in 20 mL of ethanol was heated to maintain reflux for 15 hours. After cooling, water was added and the mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (eluted with EtOAc and then 10% MeOH/EtOAc) to give 646mg (56% yield) of 1-([1,1'-biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1H-indole-3-acetic acid hydrazide, mp, 148-150°C.

Analysis f r $C_{25}H_{25}N_3O_2$:			
Calculated	C, 75.16;	H, 6.31;	N, 10.52.
Found	C, 75.14;	H, 6.40;	N, 10.63.

C. 1-([1,1'-Biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1H-indole-3-acetamide.
A mixture of 576mg (1.44 mmol) of this material and 300mg of Raney Ni in 20 mL of ethanol was heated to maintain reflux for 3 hours. After cooling the solvent was decanted and the Raney Ni washed twice with methylene chloride. The combined organic solvents were filtered and concentracted at reduced pressure and the residue was redissolved in EtOAc and washed with water. After drying ($MgSO_4$), the ethyl acetate was removed at reduced pressure and the residue was 437mg (71% yield) of 1-([1,1'-biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1H-indole-3-acetamide. mp, 173-175°C.

Analysis for $C_{25}H_{24}N_2O_2$:			
Calculated	C, 78.10;	H, 6.29;	N, 7.29.
Found	C, 78.94;	H, 6.27;	N, 7.35.

D. 1-([1,1'-Biphenyl]-2-ylmethyl)-4-hydroxy-2-methyl-1H-indole-3-acetamide.
A solution of 430mg (1.1 mmol) of 1-([1,1'-biphenyl)-2-ylmethyl)-4-methoxy-2-methyl-1H-indole-3-acetamide and 4.4 mL of 1M BBr_3/methylene chloride in 10 mL of methylene chloride was stirred for 5.5 hours. The mixture was concentrated at reduced pressure, the residue dissolved in ethyl acetate, washed with water, brine and dried ($MgSO_4$). After concentrating at reduced pressure, the residue was chromatographed on silica gel and eluted with EtOAc to give 400mg (98% yield) of 1-([1.1'-biphenyl]-2-yimethyl)-4-hydroxy-2-methyl-1H-indole-3-acetamide.
E. [[3-(2-Amino-2-oxoethyl)-1-([1,11-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid methyl ester. 1-([1,1'-Biphenyl]-2-ylmethyl)-4-hydroxy-2-methyl-1H-indole-3-acetamide (400mg, 1.08 mmol) was added to 43mg (1.08 mmol) of NaH/mineral oil in 5 mL of DMF, stirred 1 hour, 0.1 mL (1.08 mmol) of methyl 2-bromoacetate added and stirring maintained for 19 hours. The mixture was diluted with water, extracted with ethyl acetate, the ethyl acetate washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel eluting with 50% EtOAc/hexane to give 319mg (67% yield) of [[3-(2-amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid methyl ester.
F. [[3-(2-Amino-2-oxoethyl)-1-([1,11-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid sodium salt.
[[3-(2-Amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid methyl ester (319mg, 0.72 mmol) and 5 mL of 1N NaOH in 15 mL of MeOH was heated to maintain reflux for 0.5 hours, added to ethyl acetate/water and the insoluble material filtered to give 244mg (75% yield) of [[3-(2-amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid sodium salt, mp, >250°C.

Analysis for $C_{26}H_{23}N_2O_4Na$:			
Calculated	C, 89.35;	H, 5.15;	N, 6.22.
Found	C, 69.10;	H, 5.38;	N, 5.94.

Example 74

Preparation of [[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.
A. N-*tert*-butoxycarbonyl-3-methoxy-2-methylaniline.
A solution of 44.4g(344 mmol) of 3-methoxy-2-methylaniline and 75g (344 mmol)of di-*tert*-butyl dicarbonate in 400 mL of THF was heated to maintain reflux for 4 hours. After concentrating at reduced pressure, the residue was taken up in ethyl acetate, washed with 1N citric acid, water and dried ($MgSO_4$). After removing the solv nt at reduced pressure, the residue was crystallized from hexan to give 64.5g (84% yield) of N-*tert*-butoxycarbonyl-3-methoxy-2-methylaniline, mp, 56-57°C.

Analysis f r $C_{13}H_{19}NO_3$:			
Calculated	C, 65.80;	H, 8.07;	N, 5.90.
Found	C, 63.32;	H, 7.83;	N, 5.56.

B. 2-Ethyl-4-methoxy-1H-indole.

A solution of 140 mL (0.18 mol) of 1.3M *sec*-butyl lithium in cyclohexane was added slowly to N-*tert*-butoxycarbonyl-3-methoxy-2-methylaniline (21.3g, 0.09 mol) in 250 mL of THF keeping the temperaturte below -40°C with a dry ice-ethanol bath. The bath was removed and the temperature allowed to rise to 0°C and then the bath replaced. After the temperature had cooled to -60°C, 18.5g (0.18 mol) of N-methoxy-N-methylpropanamide in an equal volume of THF was added dropwise. The reaction mixture was stirred 5 minutes, the cooling bath removed and stirred an additional 18 hours. It was then poured into a mixture of 300 mL of ether and 400 mL of 0.5N HCl. The organic layer was separated, washed with water, brine, dried over $MgSO_4$, and concentrated at reduced pressure to give 25.5g of a crude of 1-[2-(*tert*-butoxycarbonylamino)-6-methoxyphenyl]-2-butanone. This material was dissolved in 250 mL of methylene chloride and 50 mL of trifluoroacetic acid and stirred for a total of 17 hours. The mixture was concentrated at reduced pressure and ethyl acetate and water added to the remaining oil. The ethyl acetate was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed three times on silica eluting with 20% EtOAc/hexane to give 13.9g of 2-ethyl-4-methoxy-1H-indole.

Analyses for $C_{11}H_{13}NO$:			
Calculated	C, 75.40;	H, 7.48;	N, 7.99.
Found	C, 74.41;	H, 7.64;	N, 7.97.

C. 2-Ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

2-Ethyl-4-methoxy-1H-indole (4.2g, 24 mmol) was dissolved in 30 mL of DMF and 960mg (24 mmol) of 60% NaH/mineral oil was added. After 1.5 hours, 2.9 mL (24 mmol) of benzyl bromide was added. After 4 hours, the mixture was diluted with water and extracted twice with ethyl acetate. The combined ethyl acetate was washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 20% EtOAc/hexane to give 3.1g (49% yield) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

D. 2-Ethyl-4-methoxy-alpha-oxo-1-(phenylmethyl)-1H-indole-3-acetamide.

Oxalyl chloride (0.87 mL, 10 mmol) was added to 2.6g (9.8 mmol) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole in 25 mL of methylene chloride, the mixture stirred for 3 hours and concentrated at reduced pressure. The residue was redissolved in 25 mL of methylene chloride, anhydrous ammonia bubbled in for 0.25 hours and the mixture concentrated. The residue was stirred with ethyl acetate/water and the insoluble material filtered. The ethyl acetate from the filtrate was washed with brine, dried ($MgSO_4$) and concentrated. The residue was washed with ether and combined with the filtered material above to give 1.19g (36% yield) of 2-ethyl-4-methoxy-*alpha*-oxo-1-phenylmethyl)-1H-indole-3-acetamide, mp, 193-199°C.

Analysis for $C_{20}H_{20}N_2O_3$:			
Calculated	C, 71.41;	H, 5.99;	N, 8.33.
Found	C, 66.22;	H, 6.16;	N, 10.42.

E. 2-Ethyl-4-methoxy-alpha-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.

A mixture of 1g(3 mmol) of 2-ethyl-4-methoxy-alpha-oxo-1-(phenylmethyl)-1H-indole-3-acetamide and 142mg (3.75 mmol) of sodium borohydride and 100 mL of ethanol was stirred for 20 hours, and evaporated at reduced pressure. The residue was taken up in ethyl acetate and water, the ethyl acetate separated and washed with brine and dried ($MgSO_4$). The solution was concentrated at reduced pressure and the residue stirred with ether. Th Insoluble material was filtered to give 893mg (88%) of 2-ethyl-4-meth xy-alpha-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 160-162°C.

Analysis for $C_{20}H_{22}N_2O_3$:			
Calculated	C, 70.99;	H, 6.55;	N, 8.28.
Found	C, 70.76;	H, 6.55;	N, 8.11.

F. 2-Ethyl-4-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide.
A solution of 875mg (2.8 mmol) of 2-ethyl-4-methoxy-alphahydroxy-1-(phenylmethyl)-1H-indole-3-acetamide and 0.51 mL (3.23 mmol) of triethylsilane in 10 mL of trifluoroacetic acid was stirred for 16 hours and concentrated at reduced pressure. The residue was taken up in ethyl acetate and water, the ethyl acetate separated, washed with brine and dried ($MgSO_4$). The residue was chromatographed on silica gel and eluted first with 50% ethyl acetate/hexane and then ethyl acetate to give 521mg (62% yield) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 152-154°C.

Analysis for $C_{20}H_{22}N_2O_2$:			
Calculated	C, 74.51;	H, 6.88;	N, 8.69.
Found	C, 74.24;	H, 6.90;	N, 8.72.

G. 2-Ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.
2-Ethyl-4-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide (483mg, 1.5 mmol) and 6 mL of BBr_3 were reacted as described in Example 56, Part C, to give after chromatography on silica gel (eluted with ethyl acetate) 156mg (34% yield) of 2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.

Analysis for $C_{19}H_{20}N_2O_2$:			
Calculated	C, 74.00;	H, 6.54;	N, 9.08.
Found	C, 69.23;	H, 6.09;	N, 8.24.

H. 2-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.
2-Ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide (135mg, 0.44 mmol) was added to 17.6mg (0.44 mmol) of NaH/mineral oil (washed with hexanes) in 5 mL of DMF, stirred 0.5 hour, 0.04 mL (0.44 mmol) of methyl 2-bromoacetate added and stirring maintained for 5 hours. The mixture was diluted with water, extracted with ethyl acetate. Some material was insoluble and was filtered. The ethyl acetate was washed with brine, dried ($MgSO_4$) and concentrated. The residue was combined with the filtered material to give 119mg (71% yield) of 2-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

Analysis for $C_{22}H_{24}N_2O_4$:			
Calculated	C, 69.46;	H, 6.36;	N, 7.36.
Found	C, 69.65;	H, 6.41;	N, 7.35.

I. 2-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.
A mixture of 100mg (0.26 mmol) of 2-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester and 2 mL of 1N NaOH in 6 mL of MeOH was heated to dissolve all materials and then stirred at room temperature for 1 hour. Water and ethyl acetate were added and the aqueous layer separated, made acidic to pH 3 with 1N HCl and ethyl acetate added. The insoluble material was filtered. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was combined with the filtered material above to give 90mg (95% yield) of 2-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid, mp, 220-222°C.

Analysis: Calc'd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 67.52; H, 5.67; N, 8.46.

Example 75

Preparation of 2-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid.

A. 1-[(3-Chlorophenyl)m thyl]-2-ethyl-4-meth xy-1H-indole 2-Ethyl-4-meth xy-1H-indole (7.65g, 44 mmol) was dissolved in 50 mL of DMF end 1.76g (44 mmol) of 60% NaH/mineral oil wes added. After 0.75 hours, 5.6 mL (24 mmol) of 3-chlorobenzyl chroride was added. After 18 hours, the mixture wes diluted with water and extracted twice with ethyl ecetate. The combined ethyl acetate was washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel end eluted with 20% EtOAc/hexene to give 1.61g (12% yield) of 1-[(3-chlorophenyl)methyl]-2-ethyl-4-methoxy-1H-indole.

B. 1-[(3-Chlorophenyl)methyl]-2-ethyl-4-methoxy-elpha-oxo 1H-indole-3-acetamide. Oxalyl chloride (0.5 mL, 5.3 mmol) was reacted with 1.6g (5.3 mmol) of 1-[(3-chlorophenyl)methyl]-2-ethyl-4-methoxy-1H-indole in 20 mL of methylene chloride end ammonia as described in Example 75, Part C and was worked up with the addition of chromatography on silica gel(eluting with ethyl acetate) to give 1.47g(75% yield) of 1-[(3-chlorophenyl)methyl]-2-ethyl-4-methoxy-alpha-oxo-1H-indole-3-acetamide, mp, 124-129°C.

Analysis for $C_{20}H_{19}ClN_2O_3$:			
Calculated	C, 64.78;	H, 5.16;	N, 7.55.
Found	C, 64.72;	H, 5.16;	N, 7.66.

C. 1-[(3-Chlorophenyl)methyl]-2-ethyl-4-methoxy-elphahydroxy-1H-indole-3-ecetamide.
Using the procedure described in Example 75, Part E, 750mg (2 mmol) of 1-[(3-chlorophenyl)methyl]-2-ethyl-4-methoxy-alpha-oxo-1H-indole-3-acetamide and 95mg (2.5 mmol) of sodium borohydride in 50 mL of ethanol were reacted to give after weshing with methylene chloride 290mg (39%) of 1-[(3-chlorophenyl)methyl]-2-ethyl-4-methoxy-*alpha*-hydroxy-1H-Indole-3-acetamide, mp, 134-136°C.

Analysie for $C_{20}H_{21}ClN_2O_3$:			
Calculated	C, 64.43;	H, 5.68;	N, 7.51.
Found	C, 65.61;	H, 5.81;	N, 11.24.

D. 1-[(3-Chlorophenyl)methyl]-2-ethyl-4-methoxy-1H-Indole-3-acetamide.
By the method in Example 75, Part F, 280mg (0.75 mmol) of 1-[(3-chlorophenyl)methyl]-2-ethyl-4-methoxy-alpha-hydroxy-1H-Indole-3-acetamide was reduced with 0.12 mL (0.75 mmol) of triethylsilane in 2 mL of trifluoroacetic acid to give by chromatography on silica gel(eluted ethyl acetate) 125mg (48% yield) of 1-[(3-chlorophenyl)methyl]-2-ethyl-4-methoxy-1H-Indole-3-ecetamide.

E. 1-[(3-Chlorophenyl)methyl]-2-ethyl-4-hydroxy-1H-Indole-3-acetamide.
1-[(3-Chlorophenyl)methyl]-2-ethyl-4-methoxy-1H-Indole-3-acetamide.
(123mg, 0.35 mmol) end 1.4 mL of BBr_3 were reected as described in Example 56, Pert C, to give efter chrometography on silica gel(eluted with ethyl ecetate) 156mg (34% yield) of 1-[(3-chlorophenyl)methyl]-2-ethyl-4-hydroxy-1H-indole-3-acetamide.

. F. [[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]ecetic acid methyl ester.
(1-[(3-Chlorophenyl)methyl]-2-ethyl-4-hydroxy-1H-Indole-3-acetamide (91mg, 0.3 mmol) wae reected with 12mg (0.3 mmol) of NeH/mineral oil (washed with hexanes) In 10 mL of DMF end then 0.03 mL (0.3 mmol) of methyl 2-bromoacetate as described in Example 75, Pert H, to give after chrometography on silica gel (eluted with ethyl ecetate) 80mg (71% yield) of 2-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-Indol-4-yl]oxy]acetic ecid methyl ester.

G. [[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic ecid. A mixture of 80mg (0.19 mmol) of [[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-Indol-4-yl]oxy]acetic ecid methyl ester end 1 mL of 1N NeOH In 3 mL of MeOH was stirred et room temperature for 1.5 hours. Water end ethyl ecetate were edded and the aqueoue leyer separated, mede acidic to pH 3 with 1N HCl. The insoluble meterial was filtered and the ethyl ecetate solution was washed with brine, dried ($MgSO_4$), and concentrated et reduced pressure. The residue was stirred with ethyl acetate end filtered and this meterial combined with the filtered material above to giv 61mg(80% yield) of [[3-(2-amino-2- xoethyl)-1-[(3-chlorophenyl)m thyl]-2-ethyl-1H-indol-4-yl]oxy]acetic ecid, mp, 216-217°C.

Analysis for $C_{21}H_{21}ClN_2O_4$:			
Calculated	C, 62.92;	H, 5.28;	N, 6.99.
Found	C, 63.09;	H, 5.41;	N, 6.99.

Example 76

Preparation of 2-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.

A. 4-Methoxy-1-(phenylmethyl)-1H-indole.

4-Methoxy-1H-indole (1.5g, 10 mmol) was dissolved in 20 mL of DMF and 400mg (10 mmol) of 60% NaH/mineral oil was added. After 1 hour, 1.2 mL (10 mmol) of benzyl bromide was added. After 3.5 hours, the mixture was diluted with water and extracted twice with ethyl acetate. The combined ethyl acetate was washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 20% EtOAc/hexane to give 1.77g (75% yield) of 4-methoxy-1-(phenylmethyl)-1H-indole.

Analysis for $C_{16}H_{15}NO$:			
Calculated	C, 81.98;	H, 6.37;	N, 5.90.
Found	C, 80.71;	H, 6.24;	N, 6.09.

B. 4-Methoxy-alpha-oxo-1-(phenylmethyl)-1H-indole-3-acetamide.

Oxalyl chloride (0.63 mL, 7.2 mmol) was added to 1.7g (7.2 mmol) of 4-methoxy-1-(phenylmethyl)-1H-indole in 20 mL of methylene chloride, the mixture stirred for 1 hour and concentrated at reduced pressure. The residue was redissolved in 25 mL of methylene chloride, anhydrous ammonia bubbled in for 0.25 hours and the mixture concentrated. The residue was stirred with ethyl acetate and the insoluble material filtered to give a mixture of 1.42g of 2-ethyl-4-methox-*alpha*-oxo-1-phenylmethyl)-1H-indole-3-acetamide and ammonium chloride.

C. 4-Methoxy-*alpha*-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.

A mixture of 1.4g (4.5 mmol) of 4-methoxy-*alpha*-oxo-1-(phenylmethyl)-1H-indole-3-acetamide and 213mg (5.6 mmol) of sodium borohydride and 50 mL of ethanol was stirred for 20 hours, 213mg (5.6 mmol) of sodium borohydride added and stirred an additional 20 hours and the mixture filtered and evaporated at reduced pressure. The residue was stirred with ethyl acetate and water and the insoluble material was filtered to give 600mg (43%) of 4-methoxy-*alpha*-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 179-182°C.

Analysis for $C_{18}H_{18}N_2O_3$:			
Calculated	C, 69.66;	H, 5.85;	N, 9.03.
Found	C, 69.52;	H, 5.76;	N, 8.86.

D. 4-Methoxy-1-(phenylmethyl)-1H-indole-3-acetamide.

A solution of 600mg (1.9 mmol) of 4-methoxy-*alpha*-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide and 0.32 mL (2 mmol) of triethylsilane in 5 mL of trifluoroacetic acid was stirred for 16 hours and concentrated at reduced pressure. The residue was taken up in ethyl acetate and water, the ethyl acetate separated, washed with brine and dried ($MgSO_4$). The residue was chromatographed on silica gel and eluted first with 50% ethyl acetate/hexane and then ethyl acetate to give after crystallizing from MeOH 262mg (47% yield) of 4-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 184-187°C.

Analysis for $C_{18}H_{18}N_2O_2$:			
Calculated	C, 73.45;	H, 6.16;	N, 9.52.
Found	C, 77.20;	H, 6.80;	N, 9.13.

E. 4-Hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.

4-Methoxy-1-(phenylmethyl)-1H-indole-3-acetamide (236mg, 0.8 mmol) and 3.2 mL of BBr_3 were reacted as described in Example 56, Part C, to give after chromatography on silica gel (eluted with 50% ethyl acetate/hexane) 78mg (35% yield) of 4-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.

F. 2-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

2-Ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide(135mg, 0.44 mmol) was added to 17.6mg (0.44 mmol) of NaH/mineral oil (washed with hexenes) in 5 mL of DMF, stirred 1.5 hours, 0.04 mL (0.44 mmol) of methyl 2-bromoacetate added and stirring maintained for 3 hours. The mixture was diluted with water, extracted with ethyl acetate. The ethyl acetate was washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel eluting with 2% MeOH/ethyl acetate to give 34mg (34% yield) of 2-[[3-(2-amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

G. 2-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.

A mixture of 100mg (0.26 mmol) of 2-[[3-(2-amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester and 2 mL of 1N NaOH in 6 mL of MeOH was stirred at room temperature for 2 hours. Water and ethyl acetate were added and the aqueous layer separated, made acidic to pH 3 with 1N HCl and ethyl acetate added. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was stirred with methylene chloride and filtered to give 17mg (56% yield) of 2-[[3-(2-amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid, mp, 207-208°C.

Analysis for $C_{19}H_{18}N_2O_4$:			
Calculated	C, 67.45;	H, 5.36;	N, 8.28.
Found	C, 67.64;	H, 5.42;	N, 8.05.

Example 77

2-Cyclopropyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide.

A. 1-[2-(tert-Butoxycarbonylamino)-5-methoxyphenyl]-2-butanone.

A solution of 1.3M *sec*-butyl lithium/cyclohexane (100 mL, 0.13 mol) was added slowly to 15.17g (0.065 mol) of N-*tert*-butoxycarbonyl-4-methoxy-2-methylaniline in 230 mL of THF while keeping the temperature below -40°C with a dry ice-ethanol bath. The bath was removed and the temperature allowed to rise to -20°C and then the bath was replaced. After the temperature had cooled to -55°C, 8.4g (0.065 mol) of N-methoxy-N-methylcyclopropylcarboxamide in 20 mL of THF was added dropwise. The reaction mixture was stirred 1 hour, the cooling bath removed and stirred an additional 2 hours. It was then poured into 500 mL of water. The organic layer was separated, washed with water, dried over Na_2SO_4 and concentrated at reduced pressure. The residue was crystallized from hexane to give 15.22g (77% yield) of [2-(*tert*-butoxycarbonylamino)-5-methoxyphenyl] cyclopropyl ketone, melting at 96-97°C.

Analyses for $C_{17}H_{23}NO_4$:			
Calculated	C, 68.66;	H, 7.59;	N, 4.59.
Found	C, 66.67;	H, 7.39;	N, 4.45.

B. 2-Cyclopropyl-5-methoxy-1H-indole.

[2-(*tert*-Butoxycarbonylamino)-5-methoxyphenyl] cyclopropyl ketone (13g, 43 mmol) in 250 mL of CH_2Cl_2 and 25 mL of trifluoroacetic acid was stirred for 4 hours, washed with water, $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica (eluted with a gradient, toluene→20% EtOAc/hexane) to give 4.15g (49% yield) of 2-cyclopropyl-5-methoxy-1H-indole as an oil.

Analyses for $C_{12}H_{13}NO$:			
Calculated	C, 76.98;	H, 6.99;	N, 7.48.
Found	C, 74.46;	H, 6.73;	N, 7.55.

C. 2-Cyclopropyl-5-m thoxy-1H-indole-3-acetic acid m thyl ester.
As in Example 1, Part C, 4.46g (0.024mole) of 2-cyclopropyl-5-methoxy-1H-indole was treated with 15 mL (0.024 mol) of a 1.6M solution of *n*-butyl lithum in hexane, 24 ml (0.024 mol) of a 1M solution of $ZnCl_2$ in ether, and 12.27 mL (0.024 mol) of methyl 2-bromoacetate to give after chromatography on silica gel (5% EtOAc/toluene→15% EtOAc/toluene) 3.81g (61%) of 2-cyclopropyl-5-methoxy-1H-indole-3-acetic acid methyl ester as an oil.

Analyses for $C_{15}H_{17}NO_3$:			
Calculated	C, 69.48;	H, 6.61;	N, 5.40.
Found	C, 65.59;	H, 6.71;	N, 4.85.

D. 2-Cyclopropyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid methyl ester.
A solution of 3.8g (148 mmol) of 2-cyclopropyl-5-methoxy-1H-indole-3-acetic acid methyl ester in 50 mL of DMF was treated with 0.59g (0146 mol) of 60% NaH/mineral oil, stirred 0.5 hour, and 1.69 mL (146 mmol) of benzyl chloride added. After 20 hours, the reaction mixture was diluted with water, extracted with EtOAc, the EtOAc solution was washed four times with water and dried over Na_2SO_4. After concentrating at reduced pressure, the product was purified by chromatography on silica, eluting with a gradient, 5% EtOAc/toluene→15% EtOAc/toluene, to give 2.05g (40% yield) of 2-cyclopropyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid methyl ester as an oil.

Analyses for $C_{22}H_{23}NO_3$:			
Calculated	C, 75.62;	H, 6.63;	N, 4.01.
Found	C, 75.42;	H, 6.66;	N, 4.11.

E. 2-Cyclopropyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid hydrazide.
Using the method described in Example 3, Part C, 2.0g (5.73 mmol) of 2-cyclopropyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid methyl ester was reacted with 3 mL of hydrazine to give after crystallization from ethanol 1.48g (74% yield) of 2-cyclopropyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid hydrazide, 173-174°C.

Analyses for $C_{21}H_{23}N_3O_2$:			
Calculated	C, 72.18;	H, 6.63;	N, 12.02.
Found	C, 71.89;	H, 6.66;	N, 11.95.

F. 2-Cyclopropyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide. An ethanol solution of 1.0g(2.86 mmol) of 2-cyclopropyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid hydrazide was reacted with approximately 3g of Raney nickel as described in Example 6, Part C, and the crude product crystallized from ethanol/water to give 0.47g(49% yield) of 2-cyclopropyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 156-158°C.

Analyses: Calc'd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.68; H, 6.79; N, 8.46.

Example 78

Preparation of 2-Cyclopropyl-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.

A solution of 400mg (1.2 mmol) of 2-cyclopropyl-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide and 2 mL of 1M BBr_3/methylene chloride in 130 mL of methylene chloride was stirred for 1 hour with an ice-water bath and 3 hours at room temperature. The mixture was poured into water, 200 mL of ethyl acetate added, the organic layer separated, washed with brine and dried (Na_2SO_4). After concentrating at reduced pressure, the residue was crystallized from ethyl acetate to give 300mg (79% yield) of 2-cyclopropyl-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 174-175°C.

Analyses for $C_{20}H_{20}N_2O_2$:			
Calculated	C, 74.58;	H, 4.29;	N, 8.74.
Found	C, 75.16;	H, 4.45;	N, 8.72.

Example 79

Preparation of [3-[[3-(2-Amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid.

A. [3-[[3-(2-Amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

2-Cyclopropyl-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide (295mg.0.9 mmol) was dissolved in 10 mL of THF and 40 mL of DMF and 45mg (1.1 mmol) of 60% NaH/mineral oil added. After 0.17 hours, 250mg (1.1 mmol) of (3-bromopropyl)phosphonic acid dimethyl ester was added and stirring maintained for 6.5 hours. The mixture was diluted with water and ethyl acetate, the organic layer separated, washed with water, brine and dried (Na_2SO_4). The solution was evaporated at reduced pressure and the residue chromatographed on silica gel eluting with a gradient, 1% MeOH/methylene chloride→5% MeOH/methylene chloride, to give 280mg (71% yield) of [3-[[3-(2-amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

B. [3-[[3-(2-Amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid. A solution of 280mg (0.6 mmol) of [3-[[3-(2-amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester and 1 mL (7.6 mmol) of trimethylsilyl bromide in 20 mL of methylene chloride was stirred for 19 hours and concentrated at reduced pressure. The residue was dissolved in 10 mL of MeOH, stirred 2 hours and concentrated. This concentrate was crystallized from acetonitrile/ethyl acetate/ether to give 250mg (94% yield) of [3-[[3-(2-amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid.

Analyses for $C_{23}H_{27}N_2O_5P$:			
Calculated	C, 62.44;	H, 6.15;	N, 6.33.
Found	C, 51.19;	H, 5.37;	N, 5.09.

Example 80

Preparation of [3-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid.

A. 5-Benzyloxy-1H-Indole-3-acetic acid ethyl ester.

As in Example 1, Part C, 80g (0.358mol) of 5-methoxy-1H-indole was treated with 222 mL (0.36 mol) of a 1.6M solution of n-butyl lithum in hexane, 360 ml (0.36 mol) of a 1M solution of $ZnCl_2$ in ether, and 39.92 mL (0.36 mol) of ethyl 2-bromoacetate to give after chromatography on silica gel (toluene→5% EtOAc/toluene) 30g (27%) of 5-benzyloxy-1H-indole-3-acetic acid ethyl ester, mp, 57-59°C.

Analyses for $C_{19}H_{19}NO_3$:			
Calculated	C, 73.77;	H, 6.19;	N, 5.43.
Found	C, 73.75;	H, 6.34;	N, 4.50.

B. 5-Hydroxy-1H-indole-3-acetic acid ethyl ester.

5-Benzyloxy-1H-indole-3-acetic acid ethyl ester (8.1g, 20.3 mmol) was hydrogenated in ethanol using 3g of Raney NI in 150 mL of ethanol at approximately 40 psi ($2.78X10^5$ Pa) of hydrogen. The catalyst was filtered and th filtrate concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with a gradient, 30% ethyl acetate/hexane→50% ethyl acetate/hexane, to give 5.7g (90% yield) f 5-hydroxy-1H-indole-3-acetic acid ethyl ester.

C. [3-[[3-(2-Ethoxy-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

5-Hydroxy-1H-indole-3-acetic acid thyl ester (560mg.1,8 mmol) was dissolved in 25 mL f THF and 75 mL of DMF and 80mg (2.0 mmol) of 60% NaH/mineral oil added. After 0.17 hours, 465mg (2.0 mmol) of (3-bromopropyl)phosphonic acid dimethyl ester was added and stirring maintained for 3.0 hours. The mixture was diluted with water and ethyl acetate, the organic layer separated, washed with water, brine and dried (Na_2SO_4). The solution was evaporated at reduced pressure and tha residue chromatographed on florisil eluting with a gradient, 1% MeOH/methylene chloride→3% MeOH/methylene chloride, to give 590mg (71% yield) of [3-[[3-(2-ethoxy-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

D. [3-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl estar.

[3-[[3-(2-Ethoxy-2-oxoethyl)-1-(phenylmathyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (590mg, 1.3 mmol) was dissolved in 40 mL of toluena and 10 mL of 0.67M $(CH_3)_2AlNH_2$ in benzene/toluene were added. Tha mixture was heated at 50°C for 3.25 hours and water and 1N HCl added. The mixture was extracted with a large volume of ethyl acetate and the organic layer was washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with a gradient, 1% MeOH/methylene chloride→4% MeOH/methylene chloride, to give 450mg (80% yield) of [3-[[3-(2-amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

E. [3-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid. A solution of 450mg (1.0 mmol) of [3-[[3-(2-amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimathyl ester and 1.5 mL (11 mmol) of trimethylsilyl bromide in 25 mL of methylane chloride was stirred for 16 hours and concentrated at reduced pressure. The residua was dissolved in 10 mL of MaOH, stirred 2 hours and concentrated. This concentrate was crystallized from ethyl acetate/methanol to give 325mg (81% yield) of [3-[[3-(2-amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid.

Analyses for $C_{20}H_{23}N_2O_5P$:			
Calculated	C, 59.70;	H, 5.76;	N, 6.96.
Found	C, 58.06;	H, 5.67;	N, 6.41.

Example 81

Preparation of [[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]phosphonic acid disodium salt.

A. [[3-(2-Ethoxy-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]phosphonic acid dimethyl ester.

5-Hydroxy-1H-indole-3-acetic acid athyl ester (730mg.2.4 mmol) was dissolved in 20 mL of THF and 75 mL of DMF and 115mg (2.8 mmol) of 60% NaH/mineral oil addad. After 0.17 hours, 1.1g (4.0 mmol) of (iodomethyl)phosphonic acid dimethyl ester was added and stirring maintained for 5.5 hours. The mixture was diluted with water and ethyl acetate, the organic layer separated, washed with water, brine and dried (Na_2SO_4). The solution was evaporated at reduced pressure and tha residue chromatographed on silica gal eluting with ather to give 150mg (14% yield) of [[3-(2-ethoxy-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]phosphonic acid dimethyl ester.

B. [[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]phosphonic acid dimethyl ester.

[[3-(2-Ethoxy-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]phosphonic acid dimethyl ester (150mg, 0.3 mmol) was dissolved in 25 mL of toluene and 10 mL of O.67M $(CH_3)_2AlNH_2$ in benzene/toluene were added. The mixture was heated at 50°C for 1.25 hours and water and 1N HCl added. The mixture was extracted with a larga volume of athyl acetata and tha organic layer was washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. Tha residue was chromatographed on silica gel eluting with a gradient, 1% MaOH/mathylane chloride→3% MeOH/methylene chloride, to giva 120mg (93% yield) of [[3-(2-amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]phosphonic acid dimethyl ester.

C. [[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]phosphonic acid.

A solution of 120mg (0.28 mmol) of [[3-(2-amino-2-oxoethyl)-1-(phanylmethyl)-1H-indol-5-yl]oxy]methyl]phosphonic acid dimethyl ester and 0.5 mL of trimethylsliyl bromide in 20 mL of methylane chloride was stirred for 17 hours and concentrated at reduced pressure. The residu was dissolved in 10 mL of MeOH, stirred 2 hours and concantrated. This concentrate was chromatographed on C_{18} reversa phase column eluting with 80% MeOH/(5%HOAc) and the on a HP-20 column eluting with 10% acetonitrle/water and then 50% acetonitrile/water to give 15mg (14% yield) of [3-[[3-(2-amino-2-oxoethyl)-1-(phenylmethyl)-

1H-indol-5-yl]oxy]methyl]ph sphonic acid di sodium salt.

Example 82

Preparation of 5-Hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.

A solution of 375mg (1.23 mmol) of 5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide (Example 3) and 5 mL of 1M BBr_3/methylene chloride in 75 mL of methylene chloride was stirred for 1.25 hours, and poured into 1N HCl. The methylene chloride layer was separated, washed with brine and dried (Na_2SO_4). The solvent was removed at reduced pressure to give as residue 310mg (90% yield) of 5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide, mp, 158-160°C.

Analyses for $C_{17}H_{16}N_2O_2$:			
Calculated	C, 70.55;	H, 5.70;	N, 9.51.
Found	C, 72.84;	H, 5.75;	N, 9.99.

Example 83

Preparation of 4-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid.

A. 4-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester.

A solution of 280mg (1.0 mmol) of 5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide in 30 mL of DMSO and 10 mL of THF was treated with 45mg (1.1 mmol) of 60% NaH/mineral oil, and then with 0.16 mL (1.1 mmol) of ethyl 4-bromobutyrate. The mixture was heated in an oil bath at 60°C for 2.25 hours. It was diluted with water, extracted with EtOAc, the EtOAc solution washed with water, saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica (CH_2Cl_2→3% MeOH/CH_2Cl_2)to give 260mg (66% yield) of 4-[[3-(2-amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester.

B. 4-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid.

4-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester (260mg, 0.66 mmol) was stirred with 2 mL of 2N NaOH in 25 mL of EtOH and 5 mL of THF for 18 hours. The mixture was acidified with 5N HCl, extracted with EtOAc, the EtOAc solution washed with saturated NaCl solution and dried (Na_2SO_4). After concentrating, the residue was crystallized from methylene chloride/ethanol to give 110mg (46% yield) of 4-[[3-(2-amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid, mp, 160-163°C.

Analyses for $C_{21}H_{22}N_2O_4$:			
Calculated	C, 68.84;	H, 6.05;	N, 7.65.
Found	C, 68.98;	H, 5.89;	N, 7.82.

Example 84

Preparation of 3-[4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propane]sulfonic acid.

5-Hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide (Example 2, 300mg, 1.0 mmol) was dissolved in 50 mL of THF, 40mg (1.0 mmol) of 60% NaH/mineral oil added, stirred 0.25 hours, 125mg (1.0 mmol) of sultone added and the mixture stirred for 24 hours. The mixture was made acidic with 5N HCl and the concentrated at reduced pressure. The residue was crystallized from ethanol/water to give 145mg (35% yield) of 3-[4-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propane]sulfonic acid, mp, 218-222°C.

Analyses for $C_{21}H_{24}N_2O_{45}S$:					
Calculated	C, 60.56;	H, 5.81;	N, 6.73;	S, 7.70.	
Found	C, 53.36;	H, 5.66;	N, 5.44;	S, 3.30;	residue, 15.32.

Example 85

Preparation of 3-[4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propane]sulfonic acid.

5-Hydroxy-2-ethyl-1-(phenylmethyl)-1H-indole-3-acetamide (310mg, 1.0 mmol) was dissolved in 50 mL of THF, 50mg (1.2 mmol) of 60% NaH/mineral oil added, stirred 0.25 hours, 150mg (1.2 mmol) of sultone added and the mixture stirred for 24 hours. The mixture was acidified with 1.5 mL of 1N HCl and concentrated et reduced pressure. The residue was chromatographed on en C-18 reverse phase column (eluted with 10% (5%HOAc)/MeOH) to give 260mg(60% yield) of 3-[4-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propane]sulfonic acid.

Analyses for $C_{22}H_{28}N_2O_5S$:					
Calculated	C, 61.38;	H, 6.09;	N, 6.51;	S, 7.45.	
Found	C, 56.00;	H, 5.79;	N, 5.52;	S, 3.85;	residue, 11.60.

Example 86

Preparation of [3-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propane]phosphonic acid dimethyl ester.

A. 5-Methoxy-1-(phenylmethyl)-1H-indole-3-acetic ecid ethyl ester.

5-Methoxy-1H-indole-3-ecetic acid ethyl ester (10.1g, 41 mmol) was dissolved in 50 mL of THF and 200 mL of DMF and 1.8g (45 mmol) of 60% NeH/mineral oil were added in portions with cooling. After 0.17 hours, 5 mL (42 mmol) of benzyl bromide wes added and stirring maintained for 1.5 hours. The mixture was diluted with water end ethyl acetate, the organic layer separated, washed with water, brine and dried (Na_2SO_4). The solution was evaporated at reduced pressure and the residue chromatographed on silica gel eluting with a gradient, 25% ethyl acetate/hexane→40% ethyl ecetate/hexane, to give 10.8g (82% yield) of 5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic ecid ethyl ester.

B. 2-Bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic acid ethyl ester.

A mixture of 5-methoxy-1-(phenylmethyl)-1H-indole-3-ecetic ecid ethyl ester (10.8g, 32 mmol) and 6.3g (35 mmol) of N-bromosuccinimide in 250 mL of carbon tetrachloride was stirred for 1.5 hours, washed with $Na_2S_2O_3$ solution, water, brine, and dried (Na_2SO_4). After concentrating et reduced pressure, the residue was chromatographed on silica gel and eluted with a gradient, 25% ether/hexane→40% ether/hexane, to give 5.5g (43% yield) of 2-bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetic ecid ethyl ester.

There was obtained a second fraction from the chromatography, 6.4g. This material was reacted with 6.3g of NBS as above end rechromatographed on silica gel eluting with 30% ether/hexane→50% ether/hexane to give 5.4g of 2,4-dibromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-ecetic ecid ethyl ester After crystallizing from methylene chloride this meterial melted at 138-140°C.

Analyses for $C_{20}H_{19}Br_2NO_3$:				
Calculated	C, 49.92;	H, 3.98;	N, 2.91;	Br, 33.21.
Found	C, 49.95;	H, 4.15;	N, 2.89;	Br, 33.52.

C. 2-Bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide.

A mixture of 4g (10 mmol) of 2-bromo-5-meth xy-1-(phenylmethyl)-1H-Indole-3-acetic acid ethyl ester and 50 mL of 0.67M $(CH_3)_2AlNH_2$/benzene/toluene in 100 mL of toluene was heated at 50°C for 7.5 hours, cooled, decomposed with ice and dilute HCl edded. Th mixture wes extracted with ethyl acetate and the ethyl acetate soluti n washed with brine, dried (Na_2SO_4), end concentrated et reduced pressure. Th re-

sidue of 2-bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide weigh d 4.0g.

D. 2-Bromo-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.

A solution of 4g (11 mmol) of 2-bromo-5-methoxy-1-(phenylmethyl)-1H-indole-3-acetamide and 35 mL of BBr_3/methylene chloride in 200 mL of methylene chloride was stirred for 1 hour, poured into ice-water, made basic with sodium bicarbonate and extracted with methylene chloride. This solution was washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel and eluted with ethyl acetate to give 1.35g (33% yield) of 2-bromo-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide.

E. [3-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester. Using the procedure described in Example 81, Part A, 1.35g (3.8 mmol) of 2-bromo-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide was reacted with 170mg (4.2 mmol) of NaH/mineral oil and then 970mg (4.2 mmol) of (3-bromoprpoyl)phosphonic acid dimethyl ester to give a product that was chromatographed on silica gel(eluted with a gradient, 1% MeOH/methylene chloride→3% MeOH/methylene chloride). There was obtained 520g (27% yield) of 3-[[3-(2-amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester, melting approximately at 100°C after crystallizing from methylene chloride/ether.

Analyses for $C_{22}H_{26}BrN_2O_5P$:				
Calculated	C, 51.88;	H, 5.15;	N, 5.50;	Br, 15.69.
Found	C, 47.83;	H, 4.83;	N, 4.85;	Br, 20.07.

Example 87

Preparation of 3-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid monomethyl ester.

A mixture of 255mg (0.5 mmol) of 3-[[3-(2-amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester and 2 mL of 2N NaOH in 20 mL of MeOH was heated to maintain reflux for 23 hours, diluted with water and extracted with ethyl acetate. The aqueous layer was made acidic with 5N HCl and extracted with ethyl acetate. The ethyl acetate was washed with brine, dried (Na_2SO_4) and evaporated at reduced pressure to give 210mg (84% yield) of 3-[[3-(2-amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid monomethyl ester.

Analyses for $C_{21}H_{24}BrN_2O_5P$:				
Calculated	C, 50.92;	H, 4.58;	N, 5.66;	Br, 16.09.
Found	C, 50.08;	H, 4.68;	N, 4.18;	Br, 17.33.

Example 88

Preparation of 3-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid.

A solution of 750mg (1.5 mmol) of 3-[[3-(2-amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester and 2 mL (15 mmol) of trimethylsilyl bromide in 75 mL of methylene chloride was stirred for 18.5 hours and concentrated at reduced pressure. The residue was dissolved in 75 mL of methanol stirred for 1.5 hours and concentrated. The residue was crystallized from ethyl acetate/ethanol/methylene chloride to give 285mg(39% yield) of 3-[[3-(2-amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid, mp, 188-190°C.

Analyses for $C_{20}H_{22}BrN_2O_5P$:				
Calculated	C, 49.91;	H, 4.61;	N, 5.82;	Br, 15.53.
Found	C, 47.99;	H, 4.73;	N, 5.37;	Br, 17.80.

The filtrate from the abov crystallization was concentrated at reduced pressure and the residue chro-

matographed on a C-18 reverse phas column eluting with 5% (5% HOAc)/MeOH. This fracti n was dissolved in 0.05N NaOH and put on e medium pressure HP-20 column and eluted with 10% acetonitrile/water->50% ecetonitrile/water to give 195mg of 3-[[3-(2-amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid disodium salt.

Analyses for $C_{20}H_{20}BrN_2O_5PNa_2$:				
Calculated	C, 46.51;	H, 3.90;	N, 4.83;	Br, 14.00.
Found	C, 45.73;	H, 3.84;	N, 5.33;	Br, 15.16.

Example 89

Preparation of 2-Bromo-6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetamide.

A. 6-Chloro-5-methoxy-1H-indole-3-acetic acid methyl ester.

Using the procedure in Example 1, Part C, 5.2g (28.6 mmol) of 6-chloro-5-methoxy-1H-indole was reacted with 18.13 mL (29 mmol) of n-butyl lithium and 29 mL of 1N $ZnCl_2$/ether and then 2.75 mL of methyl 2-bromoacetate to give a product that was chromatographed on silica gel(eluted with 5% EtOAc/toluene→10% EtOAc/toluene). There was obtained 4.66g (64% yield) of 6-chloro-5-methoxy-1H-indole-3-ecetic ecid methyl ester es an oil

Analyses for $C_{12}H_{12}ClNO_3$:			
Calculated	C, 56.82;	H, 4.77;	N, 5.52.
Found	C, 56.61;	H, 4.81;	N, 5.52.

B. 6-Chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetic acid methyl ester.

6-Chloro-5-methoxy-1H-indole-3-acetic acid methyl ester (2.0g, 8 mmol) was dissolved in 75 mL of DMF and 20 mL of THF, 340mg (8.5 mmol) of 60% NaH/mineral oil added, stirred 0.17 hours and 1.1 mL (9.2 mmol) of benzyl bromide added. After 0.75 hours, the mixture was added to water, extracted with ethyl acetate, the ethyl acetate solution washed with water, brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 20% ether/hexane→50% ether/hexene to give 1.8g (67% yield) of 6-chloro-5-methyoxy-1-(phenylmethyl)-H-indole-3-acetic acid methyl ester after crystallization from ether/hexane, mp, 64-66°C.

Anelyses for $C_{19}H_{18}ClNO_3$:				
Calculated	C, 66.38;	H, 5.08;	N, 4.07;	CL, 10.31.
Found	C, 66.37;	H, 5.25;	N, 4.13;	Cl, 10.07.

C. 2-Bromo-6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetic acid methyl ester.

A mixture of 1.0g (3.0 mmol) of 6-chloro-5-methyoxy-1-(phenylmethyl)-H-indole-3-acetic acid methyl ester and 600mg (3.3 mmol) of NBS in 100 mL of carbon tetrachloride was stirred for 30 hours. The mixture was washed with $Na_2S_2O_3$ solution, brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with a gradient, 20% ether/hexane→100% ether, to give 1.0g (79% yield) of 2-bromo-6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetic acid methyl ester that melted at 133-134°C after crystallization from methylene chloride/ether.

Analyses for $C_{19}H_{17}BrClNO_3$:					
Calculated	C, 53.99;	H, 4.05;	N, 3.31;	Br, 18.90;	Cl, 8.40.
Found	C, 54.70;	H, 4.11;	N, 3.38;	Br, 16.04;	Cl, 9.97.

D. 2-Bromo-6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetamide.

A mixture of 950mg (2.18 mmol) of 2-bromo-6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetic acid methyl ester and 20 mL of 0.67M $(CH_3)_2AlNH_2$/benzene/toluene in 75 mL of benzene was heated at 50°C

for 1.5 hour, cooled, decomposed with ice and dilute HCl add d. The mixture was extracted with ethyl acetate and the ethyl acetate solution washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure. The residue of was crystallized from ethanol/methylene chloride to give 580mg (65% yield) of 2-bromo-6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetamide, mp, 205°C (decomposition).

Analyses for $C_{18}H_{16}BrClN_2O_2$:					
Calculated	C, 53.03;	H, 3.96;	N, 6.87;	Br, 19.60;	Cl, 8.70.
Found	C, 53.72;	H, 4.42;	N, 6.97;	Br, 19.26;	Cl, 9.36.

Example 90

Preparation of 2-Bromo-6-chloro-5-hydroxy-1-(phenylmethyl)-H-indole-3-acetamide.

A solution of 730mg (1.8 mmol) of 2-bromo-6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetamide and 10 mL of 1N BBr_3/methylene chloride in 75 mL of methylene chloride was stirred for 2.5 hours, 1N HCl added and stirred. The organic solution was separated, washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 2% MeOH/methylene chloride→4% MeOH/methylene chloride to give 280mg (45% yield) of 2-bromo-6-chloro-5-hydroxy-1-(phenylmethyl)-H-indole-3-acetamide, mp, 195°C(decomposition).

Analyses for $C_{17}H_{14}BrClN_2O_2$:					
Calculated	C, 51.87;	H, 3.59;	N, 7.17;	Br, 20.30;	Cl, 9.01.
Found	C, 50.96;	H, 3.66;	N, 6.69;	Br, 19.48;	Cl, 9.49.

Example 91

Preparation of 4-[[3-(2-Amino-2-oxoethyl)-2-bromo-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid.

A. 4-[[3-(2-Amino-2-oxoethyl)-2-bromo-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester.

Using the procedure in Example 83, Part A, 235mg (0.6 mmol) of 2-bromo-6-chloro-5-hydroxy-1-(phenylmethyl)-H-indole-3-acetamide was treated with 25mg (0.6 mmol) of 60% NaH/mineral oil and then 0.1 mL (0.7 mmol) of ethyl 4-bromobutyrate to give a product that was chromatographed on silica gel. A gradient of methylene chloride→2% MeOH/methylene was used to elute 210mg (69% yield) of 4-[[3-(2-amino-2-oxoethyl)-2-bromo-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester.

B. 4-[[3-(2-Amino-2-oxoethyl)-2-bromo-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid. A mixture of 210mg (0.41 mmol) of 4-[[3-(2-amino-2-oxoethyl)-2-bromo-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid ethyl ester and 2 mL of 2N NaOH in 5 mL of THF and 25 mL of ethanol was stirred for 10.5 hours, the mixture made acidic with 5N HCl and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was crystallized from methylene chloride/ethanol to give 60mg (31% yield) of 4-[[3-(2-amino-2-oxoethyl)-2-bromo-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid, 220°C(decomposition).

Analyses for $C_{21}H_{20}BrClN_2O_4$:						
Calculated	C, 52.57;	H, 4.20;	N, 5.84;	Br, 16.65;	Cl, 7.39.	
Found	C, 54.03;	H, 4.45;	N, 5.80;	Br, 11.57;	Cl, 8.96;	residue, 1.35.

Example 92

Preparation of 3-[4-[[3-(2-Amino-2-oxoethyl)-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid.

A. 6-Chloro-5-meth xy-1-(phenylm thyl)-H-indole-3-acetamide. By the method in Example 89, Part D, 1.1g (3.2 mmol) of 6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetic acid methyl ester (Example 89, Part B) and 20 mL of $(CH_3)_2AlNH_2$/benzene/toluene in 40 mL of benzene were reacted to give 970mg (88% yield) of 6-chloro-5-methyoxy-1-(phenylmethyl)-H-indole-3-acetamide.

B. 6-Chloro-5-hydroxy-1-(phenylmethyl)-H-indole-3-acetamide. A solution of 970mg (2.8 mmol) of 6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetamide and 10 mL of 1N BBr_3/methylene chloride in 100 mL of methylene chloride was stirred for 5 hours, 1N HCl added and stirred. The organic solution was separated, washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 1% MeOH/methylene chloride→3% MeOH/methylene chloride to give 470mg (53% yield) of 6-chloro-5-hydroxy-1-(phenylmethyl)-H-indole-3-acetamide.

C. 3-[4-[[3-(2-Amino-2-oxoethyl)-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester. Using the method in Example 80, Part C, 470mg (1.5 mmol) of 6-chloro-5-hydroxy-1-(phenylmethyl)-H-indole-3-acetamide was reacted with 75mg (1.8 mmol) of 60% NaH/mineral oil end 415mg (1.8 mmol) of (3-bromopropyl)phosphonic acid dimethyl ester to give a product that was chromatographed on silica gel. On eluting with 1% MeOH/methylene chloride→4% MeOH/methylene chloride, there was obtained 400mg (57% yield) of 3-[4-[[3-(2-amino-2-oxoethyl)-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

D. 3-[4-[[3-(2-Amino-2-oxoethyl)-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid. 3-[4-[[3-(2-Amino-2-oxoethyl)-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester 400mg (0.86 mmol) was treated with 1 mL of trimethylsilyl bromide in 30 mL of methylene chloride as in Example 80, Part E, to give after crystallizing from acetonitrile/ethyl acetate/ether, 235mg (63% yield) of 3-[4-[[3-(2-amino-2-oxoethyl)-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid.

Analyses for $C_{20}H_{22}ClN_2O_5P$:				
Calculated	C, 54.99;	H, 5.08;	N, 6.41;	Cl, 8.12.
Found	C, 49.82;	H, 5.03;	N. 7.71;	Cl, 9.86.

Example 93

Preparation of 4-Allyl-2-ethyl-5-hydroxy-1-(phenylmethyl)-1H-indole-acetamide.

A. 5-Allyloxy-2-ethyl-1-(phenylmethyl)-1H-indole-acetamide. 2-Ethyl-5-hydroxy-1-(phenylmethyl)-1H-indole-acetamide (620mg, 2.0 mmol, Example 9) was dissolved in 10 mL of THF end 40 mL of DMF, 90mg (2.2 mmol) of 60% NaH/mineral oil added and after stirring 0.17 hours, 0.2 mL (2.3 mmol) of allyl bromide was added. After 2 hours, the mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried (Na_2SO_4) end concentrated et reduced pressure. The residue was chrometographed on silica gel(eluted with 1% MeOH methylene chloride→3% MeOH/methylene chloride) to give 770mg of 5-allyloxy-2-ethyl-1-(phenylmethyl)-1H-indole-acetamide.

B. 4-Allyl-2-ethyl-5-hydroxy-1-(phenylmethyl)-1H-indole-acetamide. 5-Allyloxy-2-ethyl-1-(phenylmethyl)-1H-indole-acetamide (770mg, 2.21 mmol) in 20 mL of N,N-dimethyleniline were heated in an oil bath at 190°C for 20 hours. The mixture was cooled, diluted with ethyl acetate, washed with 1N HCl, brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 1% MeOH methylene chloride→3% MeOH/methylene chloride to give 295mg (38% yield) of 4-allyl-2-ethyl-5-hydroxy-1-(phenylmethyl)-1H-indole-acetamide.

Analyses for $C_{22}H_{24}N_2O_2$:			
Calculated	C, 75.83;	H, 6.74;	N, 8.04.
Found	C, 75.70;	H, 7.05;	N, 8.06.

Example 94

Preparation of [3-[[4-Allyl-3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid disodium salt.

A. [3-[[4-Allyl-3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid

dimethyl ester.

Using the method in Example 80, Part C, 265mg (0.8 mmol) of 4-allyl-2-ethyl-5-hydroxy-1-(phenylmethyl)-1H-indole-acetamide was reacted with 40mg (1.0 mmol) of 60% NaH/mineral oil and 230mg (1.0 mmol) of (3-bromopropyl)phosphonic acid dimethyl ester to give a product that was chromatographed on silica gel. On eluting with 1% MeOH/methylene chloride→4% MeOH/methylene chloride, there was obtained 310mg (78% yield) of [3-[[4-allyl-3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester.

B. [3-[[4-Allyl-3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid disodium salt.

A solution of 310mg (0.62 mmol) of [[3-allyl-3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester and 1.0 mL (7.8 mmol) of trimethylsilyl bromide in 20 mL of methylene chloride was stirred for 18.5 hours and concentrated at reduced pressure. The residue was dissolved in 20 mL of MeOH, stirred 2.5 hours and concentrated. This residue was chromatographed on a C_{18} reverse phase column and eluted with 10%(5% HOAc)/MeOH. Material from this column was dissolved in 1N NaOH and chromatographed on a HP20 column. The product was eluted with 10% acetonitrile/water, then 25% acetonitrile/water to give 165mg (52% yield) of [3-[[4-allyl-3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid disodium salt.

Analyses for $C_{25}H_{29}N_2O_5PNa_2.3H_2O$:			
Calculated	C, 52.82;	H, 6.21;	N, 4.93.
Found	C, 52.15;	H, 5.50;	N, 4.65.

Example 95

Preparation of 2-Methyl-5-phenoxy-1-(phenylmethyl)-1H-indole-3-acetamide.

5-Hydroxy-2-methyl-1-(phenylmethyl)-1H-indole-3-acetamide (1.2g, 4.1 mmol) was dissolved in 40 mL of pyridine, 90mg (2.2 mmol) of 60% NaH/mineral oil added, stirred 0.17 hours, 315mg of CuO added, stirred 0.17 hours and 0.5(4.1 mmol) mL of Iodobenzene added. The mixture was heated to maintain reflux for 24 hours, cooled, and diluted with ethyl acetate and 1N HCl. The mixure was filtered thru a celite pad and the organic material separated, washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 1% MeOH/methylene chloride→3% MeOH/methylene chloride to give 40mg (3% yield) of 2-methyl-5-phenoxy-1-(phenylmethyl)-1H-indole-3-acetamide.

Example 96

Preparation of 2-[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid methyl ester.

Using the procedure in Example 83, Part A, 300mg (1.0 mmol) of 5-hydroxy-2-methyl-1-(phenylmethyl)-H-indole-3-acetamide was treated with 45mg (1.1 mmol) of 60% NaH/mineral oil and then 250m (1.1 mmol) of methyl 2-(bromomethyl)benzoate to give a product that was chromatographed on silica gel. A gradient of methylene chloride→2% MeOH/methylene was used to elute 270mg (69% yield) of 2-[[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid methyl ester, mp, 178-180°C.

Analyses for $C_{27}H_{26}N_2O_4$:			
Calculated	C, 73.28;	H, 5.92;	N, 6.33.
Found	C, 72.29;	H, 5.93;	N, 6.03.

Example 97

Preparation of 2-[[[3-(2-Amino-2-oxoethyl)-2-m thyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]m thyl]benzoic acid.

A mixture of 195mg (0.44 mmol) of 2-[[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid methyl ester and 2 mL of 2N NaOH in 10 mL of THF and 35 mL of ethanol was stirred for 17.5 h urs, th mixture made acidic with 5N HCl and xtracted with ethyl acetate. The ethyl acetate solution

was washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was crystallized from methylene chloride to give 110mg (59% yield) of 2-[[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid, mp, 173-176°C.

Analyses for $C_{26}H_{24}N_2O_4$:

Calculated C, 72.88; H, 5.65; N, 6.54.

Found: C, 71.90; H, 5.63; N, 6.13.

Example 98

Preparation of 2-[[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid methyl ester.

Using the procedure in Example 83, Part A, 620mg (2.0 mmol) of 5-hydroxy-2-ethyl-1-(phenylmethyl)-H-indole-3-acetamide was treated with 90mg (2.2 mmol) of 60% NaH/mineral oil and then 505mg (2.2 mmol) of methyl 2-(bromomethyl)benzoate to give a product that was chromatographed on silica gel. A gradient of 1% MeOH/methylene chloride→2% MeOH/methylene was used to elute 160mg (18% yield) of 2-[[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid methyl ester, mp, 132-134°C.

Analyses for $C_{28}H_{28}N_2O_4$:			
Calculated	C, 73.66;	H, 8.18;	N, 6.14.
Found	C, 74.36;	H, 6.20;	N, 5.82.

Example 99

Preparation of 2-[[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid.

A mixture of 495mg (1.08 mmol) of 2-[[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid methyl ester and 2 mL of 5N NaOH in 25 mL of ethanol was stirred for 17 hours, the mixture made acidic with 5N HCl and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was crystallized from methylene chloride/ether to give 440mg (92% yield) of 2-[[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid, mp, approximately 100°C.

Example 100

Preparation of 3-[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid methyl ester.

Using the procedure in Example 83, Part A, 910mg (3.0 mmol) of 5-hydroxy-2-methyl-1-(phenylmethyl)-H-indole-3-acetamide was treated with 135mg (3.3 mmol) of 60% NaH/mineral oil and then 760m (3.3 mmol) of methyl 3-(bromomethyl)benzoate to give a product that was chromatographed on silica gel. A gradient of 1% MeOH/methylene chloride→3% MeOH/methylene was used to elute a product that was recrystallized from methylene chloride/ethanol. A yield of 885mg (69%) of 3-[[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid methyl ester was obtained, mp, 147-149°C.

Analyses for $C_{27}H_{26}N_2O_4$:			
Calculated	C, 73.28;	H, 5.92;	N, 6.33.
Found	C, 73.03;	H, 5.86;	N, 6.22.

Example 101

Preparation of 3-[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid.

A mixture of 470mg (1.06 mmol) f 3-[[[3-(2-amino-2-oxoethyl)-2-m thyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid m thyl ester and 2 mL of 2N NaOH in 10 mL of THF and 40 mL of ethanol was stirred for 7.5 hours, th mixture made acidic with 5N HCl and xtracted with ethyl acetate. The thyl acetate solution was washed with brine, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was crystallized

from methylen chloride/ethanol to givs 330mg (72% yield) of 3-[[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid, mp, 176-179°C.

Analyses for $C_{26}H_{24}N_2O_4$:			
Calculeted	C, 72.88;	H, 5.65;	N, 6.54.
Found	C, 70.01;	H, 5.55;	N, 6.11.

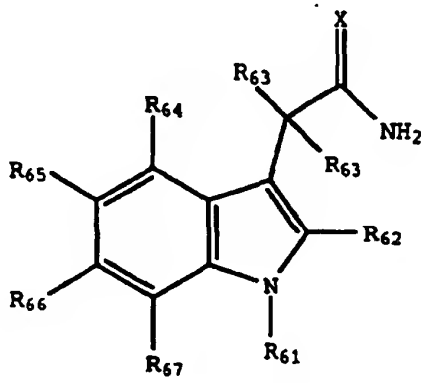
Therapeutic use of 1H-indole-3-acetamides

Tests of the 1H-indole-3-acetamides described herein have shown they achieve their beneficial therapeutic action principally by direct inhibition of human $sPLA_2$, and not by acting as antagonists for erachidonic acid, nor other active agents below arachidonic ecid in the arachidonic acid cascade, such as 5-lipoxygeneses, cyclooxygenases, and etc.

The method of the invention for inhibiting $sPLA_2$ mediated release of fatty ecids comprises contacting $sPLA_2$ with en therapeutically effective amount of the 1H-indole-3-ecetamides of the invention and pharmaceutically acceptable salts thereof.

A preferred method of the invention comprises contacting $sPLA_2$ with an therapeutically effective amount of 1H-indole-3-acetamide and pharmaceutically ecceptable salts thereof where said acetamide is substituted et the 4 and/or 5 position with an -oxyalkyl ecid, -oxyelkyl ester, -oxyalkylamine, -oxybenzyl (where the phenyl group of the benzyl radical is substituted with an acid group, ester group, amine group, or suitable salt thereof); and is substituted at the 1 position with a benzyl or biphenyl group and pharmaceutically acceptable salts thereof. Stiil another preferred method of the invention comprises contacting $sPLA_2$ with an therapeutically effective amount of 1H-indole-3-acetamide, where said ecetamide is substituted at the 4 end/or 5 position with an ecidic group, and is substituted at the 2 position with a group containing oxygen, nitrogen or sulfur group, and pharmaceutically acceptable salts thereof.

The preferred novel compounds of this invention are most preferably used for practicing the method of inhibiting $sPLA_2$ mediated release of fatty acids. This method comprises contacting $sPLA_2$ with en therapeutically effective amount of 1H-indole-3-acetamide and pharmaceutically acceptable salts thereof, represented by the formula (VI):



(VI)

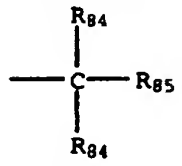
X is oxygen or sulfur;

R_{61} is selected from groups (i), (ii) and (iii) where;

(i) is C_6-C_{20} alkyl, C_6-C_{20} alkenyl, C_6-C_{20} alkynyl, C_6-C_{20} haloalkyl, C_4-C_{12} cycloalkyl, or

(ii) is aryl or aryl substituted by halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxylthio, carboxyl, amino, or hydroxyamino;

(iii) is

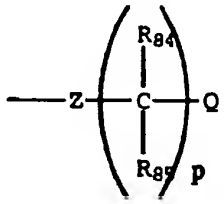


where R_{84} is hydrogen or C_1-C_{10} alkyl, and R_{85} is selected from the group: phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, nitro, phenyl, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, amino, hydroxyamino or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

R_{82} is hydrogen, halo, C_1-C_3 alkyl, ethenyl, cyclopropyl, C_1-C_2 alkylthio, C_1-C_2 alkoxy, -CHO, -CN;

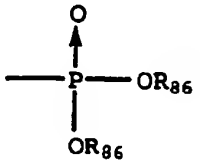
each R_{83} is independently hydrogen, or halo;

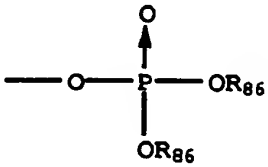
R_{84}, R_{85}, R_{86}, and R_{87} are each independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in the set R_{84}, R_{85}, R_{86}, and R_{87}, combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN, -S(C_1-C_{10} alkyl), arylthio, thioacetal, -C(O)O(C_1-C_{10} alkyl), hydrazide, hydrazino, hydrazido, $-NH_2$, $-NO_2$, $-NR_{82}R_{83}$, and $-C(O)NR_{82}R_{83}$, where, R_{82} and R_{83} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{82} and R_{83} form a 5 to 8 membered heterocyclic ring; or a group having the formula;

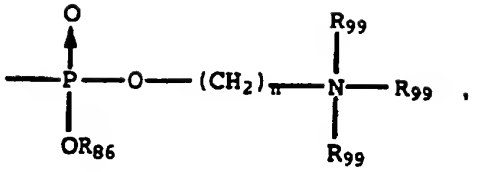


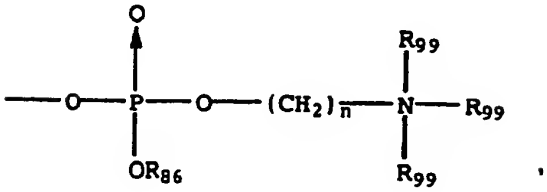
where,

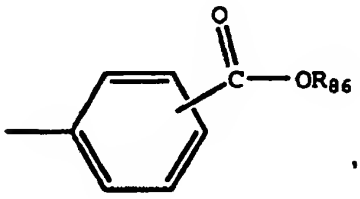
R_{84} and R_{85}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and
Q	is -CON($R_{82}R_{83}$), -5-tetrazolyl, $-SO_3H$,

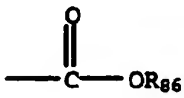


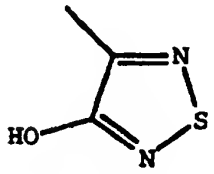












where n is 1 to 8, R_{86} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

Another aspect of this invention is a method for treating septic shock in humans which comprises administering to a human a therapeutically effective dose of 1H-indole-3-acetamide and pharmaceutically acceptable salts thereof. A preferred method for treating septic shock is to administer to humans either (1) a 1H-indole-3-acetamide substituted at the 4 and/or 5 position and substituted at the 1 position with a benzyl or biphenyl group (or a pharmaceutically acceptable salts thereof); or (2) a 1H-indole-3-acetamide substituted at the 4 and/or 5 position and substituted at the 2 position with a halogen, oxygen, nitrogen or sulfur group; or (3) a 1H-indole-3-acetamide substituted at the 4 and/or 5 position and is substituted at the 2 position with an alkyl group of 1 to 3 carbon atoms. When the 1H-indole-3-acetamide nucleus is substituted at the 4 positions the preferr d groups are selected from the group:

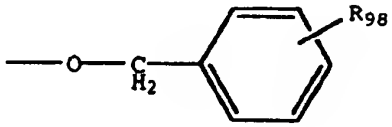
- O - CH_2 - R_{86} ,
- S - CH_2 - R_{86} ,
- NH - CH_2 - R_{86} and
- CH_2 - CH_2 - R_{86} ;

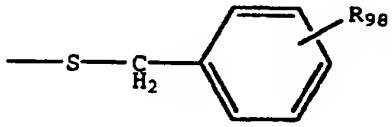
where acidic group R98 is s lect d from;

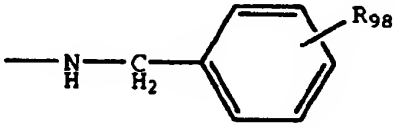
- CO_2H
- SO_3H
- $P(O)(OH)_2$

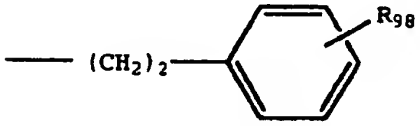
or salts, and ester derivatives
of such acidic groups.

When the 1H-indole-3-acetamide nucleus is substituted at the 5 positions the preferred groups are selected from the group:









- $O-(CH_2)_{2-4}-R_{98}$
- $S-(CH_2)_{2-4}-R_{98}$
- $NH-(CH_2)_{2-4}-R_{98}$
- $CH_2-(CH_2)_{2-4}-R_{98}$

where acidic group R_{98} is selected from;

- CO_2H
- SO_3H
- $P(O)(OH)_2$

or salts, and ester derivatives
of such acidic groups.

Pharmaceutical Formulations

As previously noted the compounds of this invention are useful for inhibiting $sPLA_2$ mediated release of fatty acids such as arachidonic acid. By the term, "inhibiting" is meant the prevention or therapeutically significant reduction in release of $sPLA_2$ initiated fatty acids by the compounds of the invention.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration and th condition being tr ated. Typical daily doses will contain a n n-toxic dosag level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

The compound can be administered by a variety of routes including rai, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the 1H-indole-3-acetamides of the invention together with a pharmaceutically acceptable carrier or diluent therefor. The compounds of the present invention are preferably formulated prior to administration.

The active ingredient in such formulations comprises from 0.1% to 99.9% by weight of the formulation. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way. The term, 'Active Ingredient", means a 1H-indole-3-acetamide compound of the invention or a pharmaceutically acceptable salt thereof.

Formulation 1

A tablet is prepared using the ingredients below:

	Quantity - (mg/capsule)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5

The components are blended and compressed to form tablets. each weighing 665 mg.

Formulation 2

An aerosol solution is prepared containing the following components:

	Weight
Active Ingredient	0.25
Ethanol	25.75
Chlorodifluoromethane propellant	74.00

The Active Ingredient is mixed with ethanol and the mixture added to a portion of the propellant, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Assay Experiments

Assay Exampl 1

The following chromogenic assay procedure was used to identify and evaluate inhibitors of recombinant

human secreted phospholipase A_2. The assay described herein has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A_2 on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992: Reagents:

REACTION BUFFER -

CaCl2.2H2O (1.47 g/L)
KCl (7.455 g/L)
Bovine Serum Albumin (fatty acid free) (1 g/L)
(Sigma A-7030, product of Sigma Chemical Co. St. Louis MO, USA)
TRIS HCl (3.94 g/L)
pH 7.5 (adjust with NaOH)

ENZYME BUFFER -

0.05 NaOAc.3H2O, pH 4.5
0.2 NaCl
Adjust pH to 4.5 with acetic acid

DTNB - 5,5"-dithiobis-2-nitrobenzoic acid

RACEMIC DIHEPTANOYL THIO - PC

racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-*sn*-glycero-3-phosphorylcholine
TRITON X-100™ prepare at 6.249 mg/ml in reaction buffer to equal 10uM.

REACTION MIXTURE -

A measured volume of racemic diheptanoyl thio PC supplied in chloroform at a concentration of 100 mg/ml is taken to dryness and redissolved in 10 millimolar TRITON X-100™ nonionic detergent aqueous solution. Reaction Buffer is added to the solution, then DTNB to give the Reaction Mixture.
The reaction mixture thus obtained contains 1mM diheptanoly thio-PC substrate, 0.29 mm Triton X-100™ detergent, and 0.12 mm DTMB in a buffered aqueous solution at pH 7.5.
Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
2. Add 10 ul test compound (or solvent blank) to appropriate wells, mix 20 seconds;
3. Add 50 nanograms of $sPLA_2$ (10 microliters) to appropriate wells;
4. Incubate plate at 40°C for 30 minutes;
5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

All compounds were tested in triplicate. Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured at 405 nanometers. Lack of color development at 405 nanometers evidenced inhibition. Compounds initially found to be active were reassayed to confirm their activity and, if sufficiently active, IC_{50} values were determined. Typically, the IC_{50} values were determined by diluting test compound serially two-fold such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC_{50} values. IC_{50} were determined by plotting log concentration versus inhibition values in the range from 10-90% inhibition. Each IC_{50} value was determined three times.
Results of Human Secreted Phospholipase A2 Inhibition Tests--Amides

Example	Inhibition of human secreted PLA_2 IC50 ± mean deviation (3-5 tests)
1	1.33 ± 0.45 uM
2	0.84 ± 0.38 uM
3	3.70 ± 2.82 uM
4	2.05 ± 0.85 uM
5	0.84 ± 0.17 uM
6	1.30 ± 0.29 uM
7	5.45 ± 1.62 uM
8	21.39 ± 8.55 uM
9	0.26 ± 0.11 uM
10	38.08 ± 2.82 uM
11	0.25 ± 0.03 uM
12	0.40 ± 0.09 uM
13	0.92 ± 0.24uM
14	8.48 ± 5.25 uM
15	1.51 ± 0.58 uM
16	1.84 ± 0.44 uM
17	1.61 ± 0.44 uM
18	0.80 ± 0.05 uM
19	1.16 ± 0.41 uM
20	1.05 ± 0.11 uM
21	0.43 ± 0.23 uM
22	0.15 ± 0.04 uM
23	0.92 ± 0.36 uM
24	0.06 ± 0.02 uM
25	3.34 ± 0.46 uM
26	2.49 uM

Example	Inhibition of human secreted PLA_2 IC50 ± mean deviation (3-5 tests)
27	3.30 ± 0.10 uM
28	1.55 ± 0.93 uM
29	1.23 ± 0.33 uM
30	3.61 ± 0.75 uM
31	0.45 ± 0.08 uM
32	12.21 ± 0.55 uM
33	0.30 ± 0.12 uM
34	7.96 ± 1.22 uM
35	2.36 ± 0.15 uM
36	7.46 ± 1.66 uM
37	9.44 ± 1.44 uM
38	0.40 ± 0.07 uM
39	1.38 ± 0.28 uM
40	0.05 ± 0.01 uM
41	0.06 ± 0.01 uM
42	0.23 ± 0.06 uM
43	0.07 ± 0.03 uM
44	0.38 ± 0.14 uM
45	1.55 ± 0.51 uM
46	0.16 ± 0.19 uM
47	0.09 ± 0.06 uM
48	>100 uM
49	0.47 ± 0.05 uM
50	2.47 ± 1.31 uM
51	8.28 ± 4.33 uM
52	0.77 ± 0.27 uM
53	0.68 ± 0.00 uM
54	0.65 ± 0.15 uM

Example	Inhibition of human secreted PLA_2 IC50 ± mean deviation (3-5 tests)
55	22.0 ± 6.0 uM
56	0.34 ± 0.10 uM
57	1.27 uM
58	0.05 ± 0.00 uM
59	0.074 ± 0.016 uM
60	0.104 ± 0.017 uM
61	0.27 uM
62	0.02 ± 0.01 uM
63	0.039 ± 0.005 uM
64	0.016 ± 0.001 uM
65	0.36 ± 0.13 uM
66	0.36 ± 0.07 uM
67	1.68 uM
68	1.45 uM; 1.12 uM
69	1.38 ± 0.52 uM
70	5.88 ± 1.17 uM
71	2.37 ± 0.79 uM
72	0.050 ± 0.15 uM
73	0.010 ± 0.001 uM
74	0.024 ± 0.002 uM
75	0.039 ± 0.004 uM
76	0.337 uM; 0.305 uM
77	0.336 ± 0.023 uM
78	0.118 ± 0.011 uM
79	0.046 ± 0.006 uM
80	0.20 ± 0.09 uM
81	3.8 uM; 3.6 uM
82	3.68 ± 0.19 uM

Example	Inhibition of human secreted PLA_2 IC50 ± mean deviation (3-5 tests)
83	0.15 ± 0.04 uM
84	0.195 ± 0.065 uM
85	0.050 ± 0.019 uM
86	0.42 ± 0.21 uM
87	0.072 ± 0.017 uM
88	0.033 ± 0.006 uM
89	0.12 ± 0.02 uM
90	0.09 ± 0.01 uM
91	0.02 ± 0.01 uM
92	0.014 ± 0.004 uM
93	0.14 ± 0.04 uM
94	0.612 ± 0.065 uM
95	1.01 ± 0.32 uM
96	0.62 ± 0.18 uM
97	0.15 ± 0.01 uM
98	1.15 ± 0.32 uM
99	0.54 ± 0.18 uM
100	3.84 ± 1.32 uM
101	1.89 ± 0.50 uM

Assay Example 2

Method:

Male Hartley strain guinea pigs (500-700g) were killed by cervical dislocation and their heart and lungs removed intact and placed in aerated (95% O_2:5% CO_2) Krebs buffer. Dorsal pleural strips (4x1x25mm) were dissected from intact parenchymal segments (8x4x25mm) cut parallel to the outer edge of the lower lung lobes. Two adjacent pleural strips, obtained from a single lobe and representing a single tissue sample, were tied at either end and independently attached to a metal support rod. One rod was attached to a Grass force-displacement transducer (Model FTO3C, product of Grass Medical Instruments Co., Quincy, MA, USA). Changes in isometric tension were displayed on a monitor and thermal recorder (product of Modular Instruments, Malvern, PA). All tissues were placed in 10 ml jacketed tissue baths maintained at 37°C. The tissue baths were continuously aerated and contained a modified Krebs solution of the following composition (millimolar) NaCl, 118.2; KCl, 4.6; $CaCl_2 \cdot 2H_2O$, 2.5; $MgSO_4 \cdot 7H_2O$, 1.2; $NaHCO_3$, 24.8; KH_2PO_4, 1.0; and dextrose, 10.0. Pleural strips from the opposite lobes of the lung were used for paired experiments. Preliminary data generated from tension/response curves demonstrated that resting tension of 800mg was optimal. The tissues were allowed to equilibrate for 45 min. as the bath fluid was changed periodically.

Cumulative concentration-response curves:

Initially tissues were challenged 3 times with KCl (40 mM) to test tissue viability and to obtain a consistent response. After recording the maximal response to KCl, the tissues were washed and allowed to return to base-

line before th next chellenge. Cumulative concentration-response curves were obtained from pleural stripe by increasing the agonist concentration ($sPLA_2$) in the tissue bath by half-log_{10} increments while the previous concentration remained in contact with the tissues (Ref.1, supra.) Agonist concentration was increased efter reaching the plateau of the contraction elicited by the preceding concentration. One concentration-response curve was obtained from each tissue. To minimize variability between tissues obtained from different enimals, contractile responses were expressed as e percentage of the maximal response obtained with the final KCl challsnge. When studying the effects of various drugs on the contractile effects of $sPLA_2$, the compounds end their respective vehicles were added to the tissues 30 min. prior to starting the $sPLA_2$ concentration-response curves.

Statistical analysis:

Data from different experiments were pooled end presented as e percentage of the maximal KCl responses (mean ± S.E.). To estimate the drug induced rightward shifts in the concentration response curves, the curves were analyzed simultaneously using statistical nonlinear modeling methods similar to those described by Waud (1976), Equation 26, p. 163, (Ref.2). The model includes four parameters: the maximum tissue response which was assumed the same for eech curve, the ED_{50} for the control curve, the steepness of the curves, end the pA_2, the concentration of antagonist that requires a two-fold increase in egonist to achieve an equivalent response. The Schild slope was determined to be 1, using statistical nonlinear modeling methods similar to those described by Waud (1976), Equation 27, p. 164 (Ref. 2). The Schild slope equal to 1 indicates the model is consistent with the essumptions of a competitive antagonist; therefore, the pA2 may be interpreted as the apparent K_B, the dissociation constant of the inhibitor.

To estimate the drug-induced suppression of the maximal responses, $sPLA_2$ responses (10 ug/ml) were determined in the absence and presence of drug, and percent auppression was calculated for each pair of tissues. Representative examples of inhibitory activities are presented in Teble 2, below.

Ref. 1 - ven, J.M.: Cumulative dose-response curves. II. Technique for the making of dose-response curves in isolated organs and the evaluation of drug parameters. Arch. Int. Pharmacodyn. Ther. 143: 299-330, 1963.

Ref. 2 - Weud, D.: Analysis of dose-response reletionships. in Advances in General and Cellular Pharmacology eds Narahashi, Blanchi 1:145-178, 1976.

TABLE 2

Compound of Example No.	Tissue Test ($sPLA_2$) Apparent K_B (uM)	%Supp(30uM)[3] (10uM^)[4]
4	22.54±3.91	10.5±23.1
5	3.43±0.88	74.9±4.2
9	5.91±0.97	49.2±9.4
12	7.93±3.52	30.3±15.2
16	4.92±0.60	51.7±4.2
18	1.98±0.35	74.1±4.0
23	2.38±0.59	83.3±2.7

Notes:

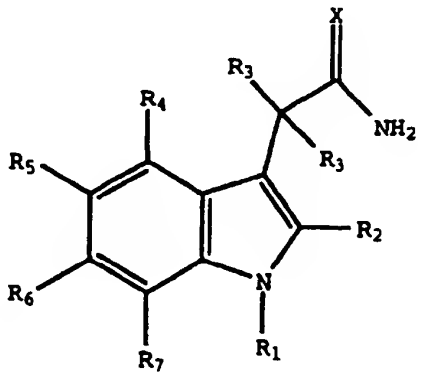
3 % suppression of $sPLA_2$ contraction at compound concentration of 30uM.

4 % suppression of $sPLA_2$ contraction at compound concentration of 10uM.

While the present invention has been illustrated above by certain specific embodiments, it is not intended that these specific examples should limit the scope of the invention as described in the appended claims.

Claims

1. A 1H-indole-3-acetamide represented by the formula (I), and pharmaceutically acceptable salts thereof;



(I)

wherein ;

X is oxygen r sulfur;

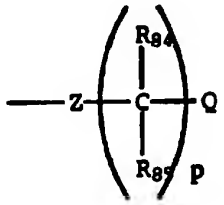
R_1 is selected from groups (i), (ii) and (iii) where;

(i) is C_6-C_{20} alkyl, C_6-C_{20} alkenyl, C_6-C_{20} alkynyl, C_6-C_{20} haloalkyl, C_4-C_{12} cycloalkyl, or
(ii) is aryl or aryl substituted by halo, -CN, -CHO, -OH, nitro, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, C_1-C_{10} alkyl, carboxyl, amino, or hydroxyamino; or
(iii) is $-(CH_2)_n-(R_{80})$, or $-(NH)-(R_{81})$, where n is 1 to 8, and R_{80} is a group recited in (i), and R_{81} is selected from a group recited in (i) or (ii);

R_2 is hydrogen, halo, C_1-C_3 alkyl, ethenyl, C_1-C_2 alkylthio, C_1-C_2 alkoxy, -CHO, or -CN;

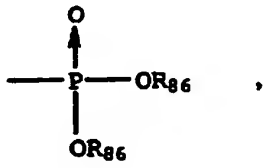
each R_3 is independently hydrogen, halo, or methyl;

R_4, R_5, R_6, and R_7 are each independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in the set R_4, R_5, R_6, and R_7, combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN, C_1-C_{10} alkyl thio, arylthio, thioacetal, $-C(O)O(C_1$-C_{10} alkyl), hydrazide, hydrazino, hydrazido, $-NH_2$, $-NO_2$, $-NR_{82}R_{83}$, and $-C(O)NR_{82}R_{83}$, where, R_{82} and R_{83} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{82} and R_{83} form a 5 to 8 membered heterocyclic ring; or
a group having the formula;



where,

R_{84} and R_{85}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, $-N(C_1$-C_{10} alkyl)-, -NH-, or -S-; and
Q	is $-CON(R_{82}R_{83})$, -5-tetrazolyl, $-SO_3H$,



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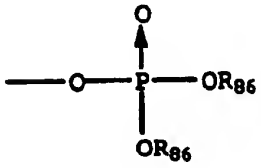

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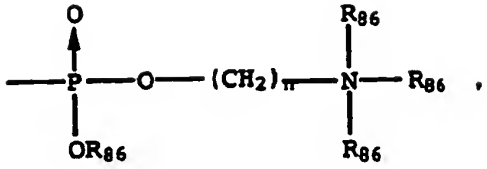
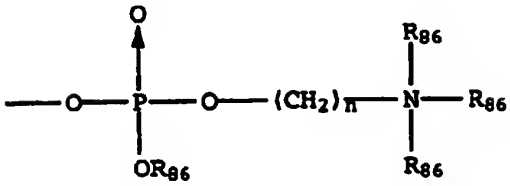
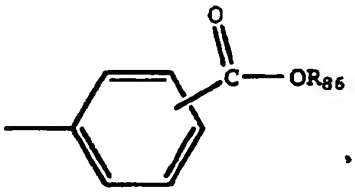
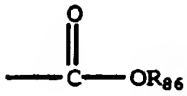
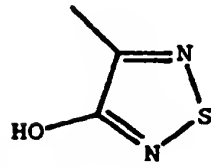




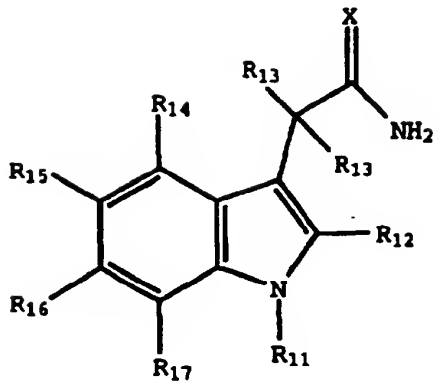






where R_{86} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl.

2. A 1H-indole-3-acetamide represented by the formula (II), and pharmaceutically acceptable salts and prodrug derivatives thereof,



(II)

wherein ;

X is oxygen or sulfur;

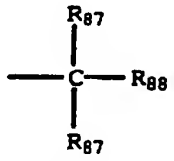
R_{11} is selected from groups (i), (ii) (iii) and (iv) where;

(i) is C_5-C_{20} alkyl, C_5-C_{20} alkenyl, C_5-C_{20} alkynyl, C_5-C_{20} haloalkyl, C_4-C_{12} cycloalkyl, or

(ii) is aryl or aryl substituted by halo, nitro, -CN, -CHO, -OH, -SH, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, carboxyl, amino, or hydroxyamino; or

(iii) is -$(CH_2)_n$-(R_{80}), or -(NH)-(R_{81}), where n is 1 to 8, and R_{80} is a group recited in (i), and R_{81} is selected from a group recited in (i) or (ii);

(iv) is



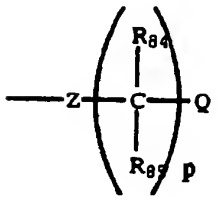
where R_{87} is hydrogen or C_1-C_{10} alkyl, and R_{88} is selected from the group; phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, phenyl, nitro, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, carboxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

R_{12} is halo, C_1-C_2 alkylthio, or C_1-C_2 alkoxy;

each R_{13} is independently hydrogen, halo, or methyl;

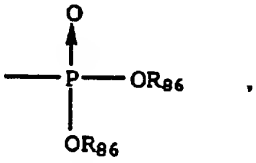
R_{14}, R_{15}, R_{16}, and R_{17} are each independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in the set R_{14}, R_{15}, R_{16}, and R_{17}, combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN, C_1-C_{10} alkylthio, arylthio, thioacetal, -C(O)O(C_1-C_{10} alkyl), hydrazide, hydrazino, hydrazido, $-NH_2$, $-NO_2$, $-NR_{82}R_{83}$, and -C(O)$NR_{82}R_{83}$, where, R_{82} and R_{83} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{82} and R_{83} form a 5 to 8 membered heterocyclic ring; or

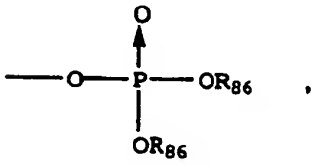
a group having the formula;

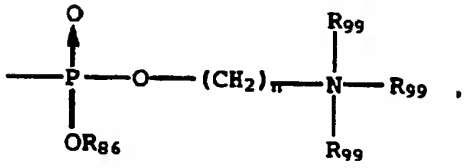


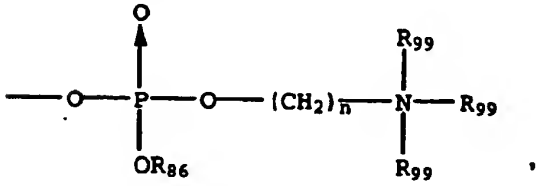
where,

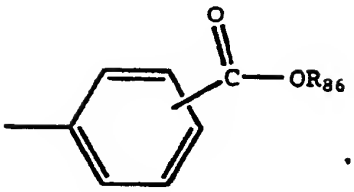
R_{84} and R_{85}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and
Q	is -CON($R_{82}R_{83}$), -5-tetrazolyl, -SO_3H,

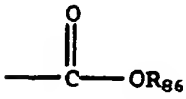


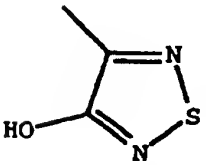






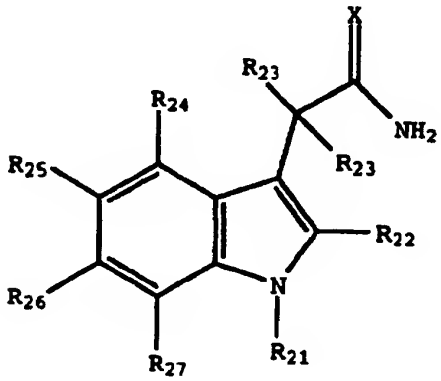






where n is 1 to 8, R_{88} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

3. A 1H-indole-3-acetamide represented by the formula (III), and pharmaceutically acceptable salts and prodrug derivatives thereof,



(III)

wherein ;

X is oxygen or sulfur;

R_{21} is $-(CH_2)_n-(R_{80})$, or $-(NH)-(R_{80})$, where n is 1 to 8, and R_{80} is aryl or aryl substituted by C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_4-C_{12} cycloalkyl, C_1-C_{10} hydroxyalkyl, carboxyl, halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, carboxyl, amino, or hydroxyamino, or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

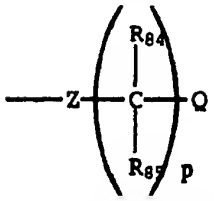
R_{22} is hydrogen, halo, C_1-C_3 alkyl, ethenyl, cyclopropyl, C_1-C_2 alkylthio, C_1-C_2 alkoxy, -CHO, -CN;

each R_{23} is independently hydrogen, halo, or methyl;

R_{24} and R_{25} are each independently selected from (a) and (b) where;

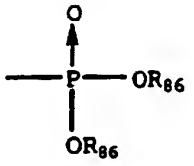
(a) is hydrogen, halo, alkyl, or alkoxy, and;

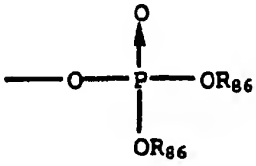
(b) is a group having the formula;

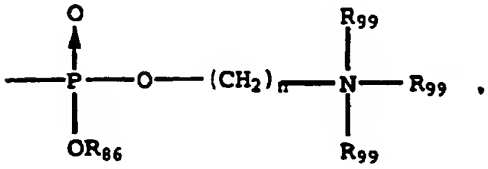


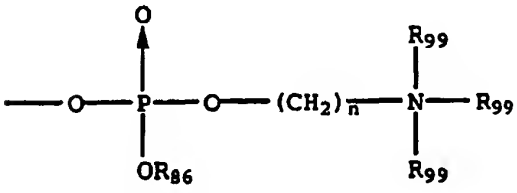
with the proviso that at least one of R_{24} and R_{25} must be selected from (b), and where;

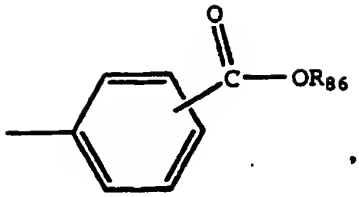
R_{84} and R_{85}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and
Q	is -CON($R_{82}R_{83}$), -5-tetrazolyl, -SO_3H,

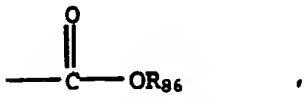


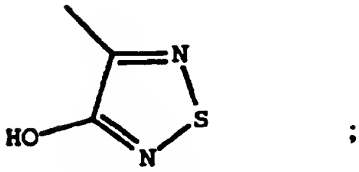








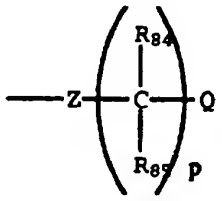




where n is 1 to 8, R_{86} is independantly selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl;

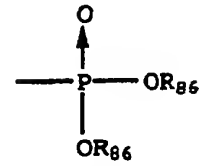
R_{26}, and R_{27} are each independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or the adjacent hydrocarbyl groups in the groups R_{26} and R_{27} combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN, C_1-C_{10} alkylthio, arylthio, thioacetal, -C(O)O(C_1-C_{10} alkyl), hydrazide, hydrazino, hydrazido, $-NH_2$, $-NO_2$, $-NR_{82}R_{83}$, and -C(O)$NR_{82}R_{83}$, where, R_{82} and R_{83} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{82} and R_{83} form a 5 to 8 membered heterocyclic ring; or

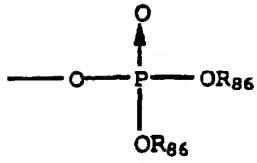
a group having the formula;

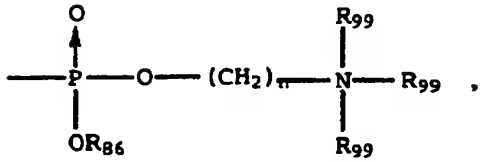


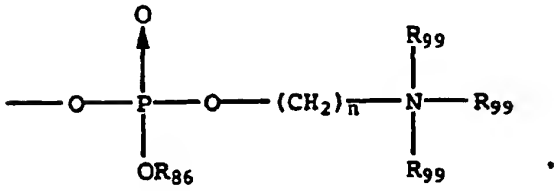
where,

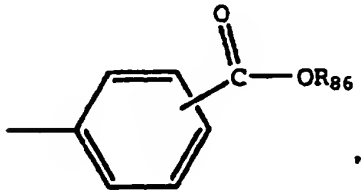
R_{84} and R_{85}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and
Q	is -CON($R_{82}R_{83}$), -5-tetrazolyl, $-SO_3H$,

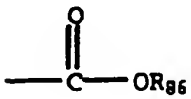


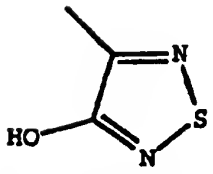








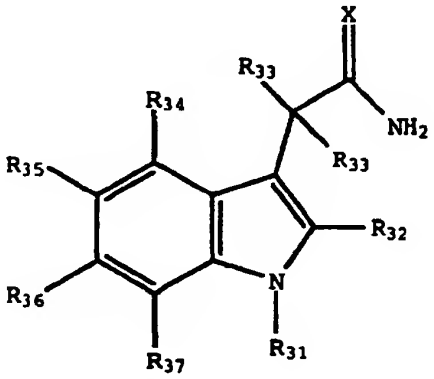




;

where n is 1 to 8, R_{88} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

4. A 1H-indole-3-acetamide represented by the formula (IV), and pharmaceutically acceptable salts and prodrug derivatives thereof,



(IV)

wherein ;

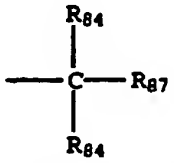
X is oxygen or sulfur;

R_{31} is selected from groups (i), (ii) and (iii) where;

(i) is C_6-C_{20} alkyl, C_6-C_{20} alkenyl, C_6-C_{20} alkynyl, C_6-C_{20} haloalkyl, C_4-C_{12} cycloalkyl, or

(ii) is aryl or aryl substituted by halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, carboxyl, amino, or hydroxyamino;

(iii) is



where R_{84} is hydrogen or C_1-C_{10} alkyl, and R_{87} is selected from the group; phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxy, carboxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

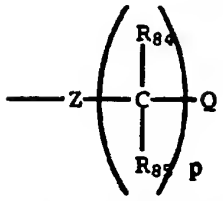
R_{32} is halo, C_1-C_2 alkylthio, C_1-C_2 alkoxy;

each R_{33} is independently hydrogen, halo, or methyl;

R_{34} and R_{35} are each independently selected from (a) and (b) where;

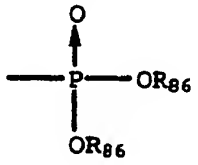
(a) is hydrogen, halo, alkyl, or alkoxy, and

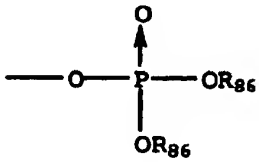
(b) is a group having the formula;

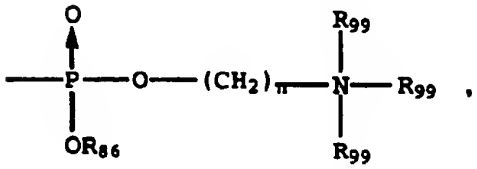


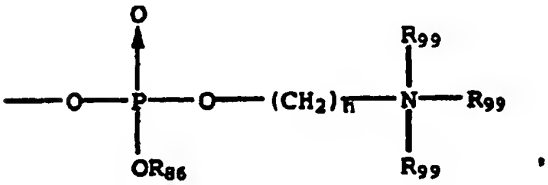
with the proviso that at least one of R_{34} and R_{35} must be selected from (b), and where:

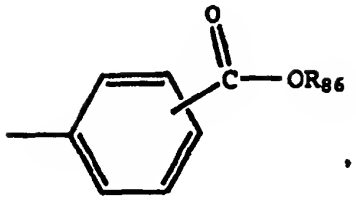
R_{84} and R_{85}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and
Q	is -CON($R_{82}R_{83}$), -5-tetrazolyl, -SO_3H,

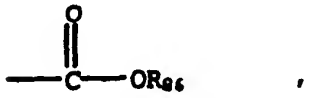


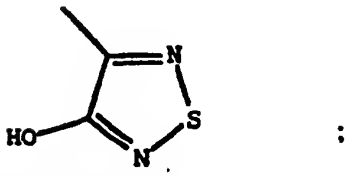






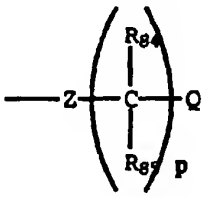






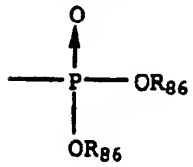
where n is 1 to 8, R_{66} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

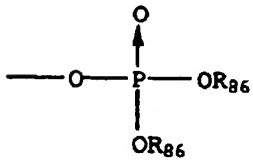
R_{36} and R_{37} are each independently hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or the adjacent hydrocarbyl groups in the groups R_{36} and R_{37} combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN, C_1-C_{10} alkylthio, arylthio, thioacetal, -C(O)O(C_1-C_{10} alkyl), hydrazide, hydrazino, hydrazido, $-NH_2$, $-NO_2$, $-NR_{62}R_{63}$, and $-C(O)NR_{62}R_{63}$, where, R_{62} and R_{63} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{62} and R_{63} form a 5 to 8 membered heterocyclic ring; or
a group having the formula:

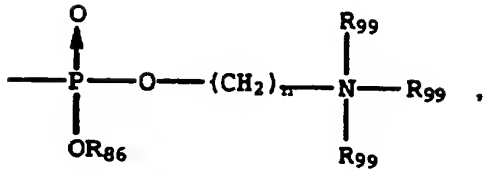


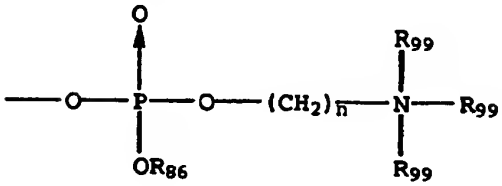
where,

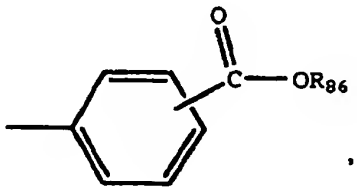
R_{64} and R_{65}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{64} and R_{65} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and
Q	is $-CON(R_{62}R_{63})$, -5-tetrazolyl, $-SO_3H$,

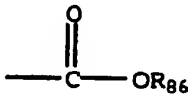


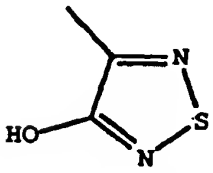






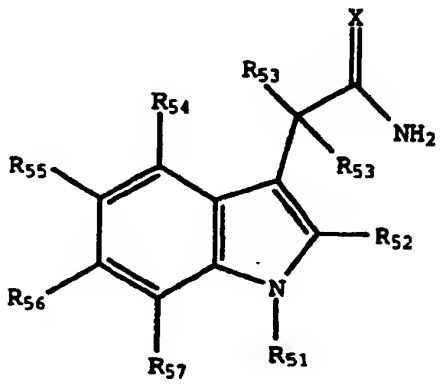






where n is 1 to 8, R_{88} is independ ntly selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

5. A 1H-indole-3-acetamid represented by the formula (V), and pharmaceutically acceptable salts and prodrug derivatives thereof,

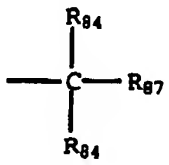


(V)

wherein;

X is oxygen;

R_{51} is



where,

R_{84} is hydrogen or C_1-C_{10} alkyl, and R_{87} is -$(CH_2)_m$-(phenyl) or -$(CH_2)_m$-(biphenyl), wherein m is 0 to 2 and the phenyl or biphenyl radicals are unsubstituted or substituted by halo, -CN, -CHO, -OH, nitro, phenyl, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkyl, C_1-C_{10} alkoxyl, carboxyl, amino, hydroxyamino or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

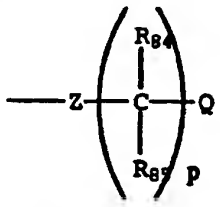
R_{52} is halo, methylthio, cyclopropyl, or C_1-C_3 alkyl;

each R_{53} is hydrogen or halo;

R_{54} and R_{55} are each independently selected from (a) and (b) where;

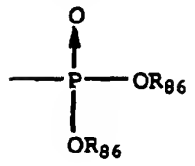
(a) is hydrogen, and;

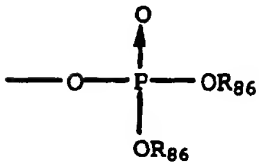
(b) is a group having the formula;

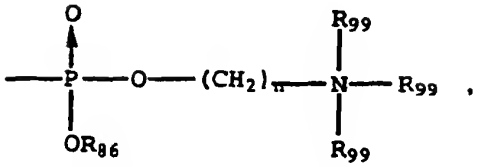


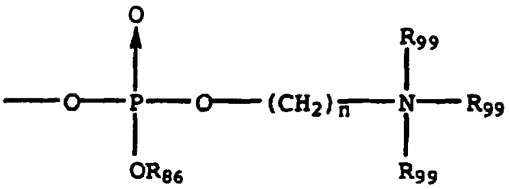
with the proviso that at least one of R_{54} and R_{55} must be selected from (b), and where;

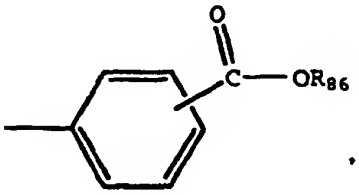
R_{84} and R_{85}	are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;
p	is 1 to 5,
Z	is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH- or -S-; and
Q	is -5-tetrazolyl, -SO_3H,

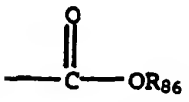






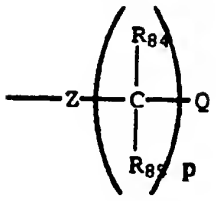






where n is 1 to 8, R_{86} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl;

R_{56}, and R_{57} are each independently hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, C_1-C_{10} haloalkyl, C_1-C_{10} alk xy, C_1-C_{10} haloalkoxy, phen xy, halo, hydroxy, carboxyl, or a group having the formula;



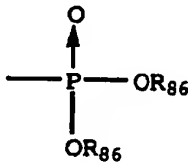
where,

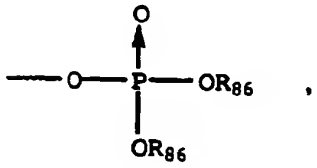
R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;

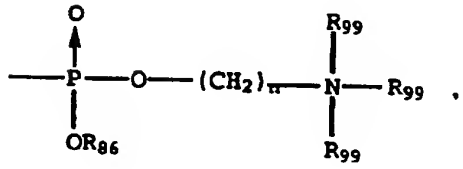
p is 1 to 5,

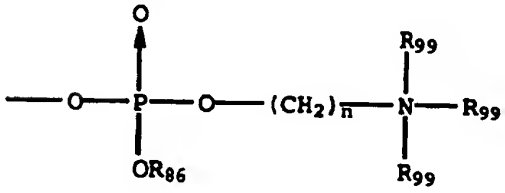
Z is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and

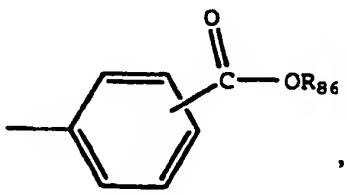
Q is -5-tetrazolyl, -SO_3H,

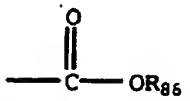








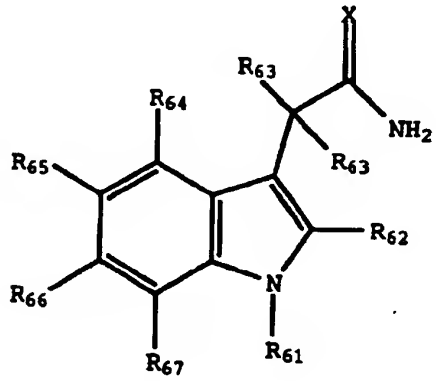




where n is 1 to 8, R_{88} is hydrogen a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

6. A pharmaceutical formulation comprising as an active ingredient, a compound as claimed in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, associated with one or more pharmaceutically acceptable carriers therefor.

7. A compound of formula (VI)



(VI)

or a pharmaceutically acceptable salt or prodrug derivative thereof for use in inhibiting $sPLA_2$ mediated release of fatty acid which comprises contacting $sPLA_2$;
wherein in formula (VI);

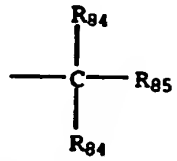
X is oxygen or sulfur;

R_{61} is selected from groups (i), (ii) and (iii) where;

(i) is C_6-C_{20} alkyl, C_6-C_{20} alkenyl, C_6-C_{20} alkynyl, C_6-C_{20} haloalkyl, C_4-C_{12} cycloalkyl, or

(ii) is aryl or aryl substituted by halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxylthio, carboxyl, amino, or hydroxyamino;

(iii) is



where R_{84} is hydrogen or C_1-C_{10} alkyl, and R_{85} is selected from the group; phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, nitro, phenyl, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring, or R_{84} and R_{85} taken together are =O;

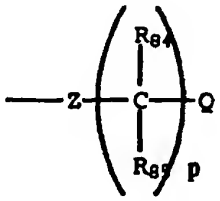
R_{62} is hydrogen, halo, C_1-C_3 alkyl, ethenyl, cyclopropyl, C_1-C_2 alkylthio, C_1-C_2 alkoxy, -CHO, -CN;

each R_{63} is independently hydrogen, or halo;

R_{64}, R_{65}, R_{66}, and R_{67} are each independently hydrogen. C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in the set R_{64}, R_{65}, R_{66}, and R_{67}, combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy,

phenoxy, hal , hydroxy, carboxyl, -SH, -CN, -S(C_1-C_{10} alkyl), arylthio, thioacetal, -C(O)O(C_1-C_{10} alkyl), hydrazide, hydrazino, hydrazido, $-NH_2$, $-NO_2$, $-NR_{62}R_{63}$, and $-C(O)NR_{62}R_{63}$, where, R_{62} and R_{63} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{62} and R_{63} form a 5 to 8 membered heterocyclic ring; or

a group having the formula;



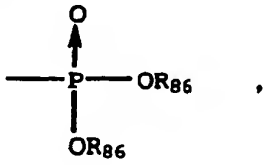
where,

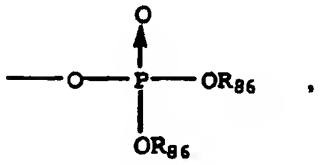
R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;

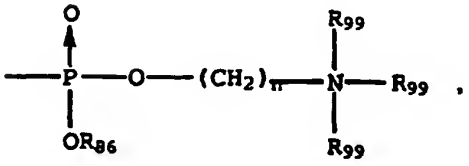
p is 1 to 5,

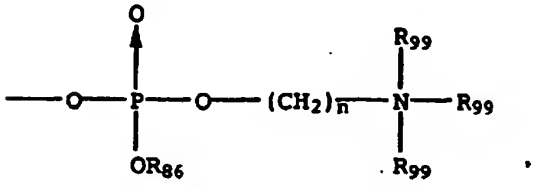
Z is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-; and

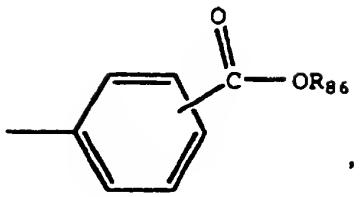
Q is $-CON(R_{62}R_{63})$, -5-tetrazolyl, $-SO_3H$,

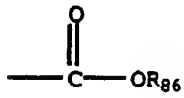


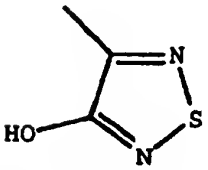












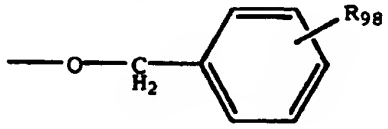
where n is 1 to 8, R_{88} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

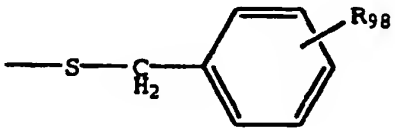
8. Use of a compound of formula (VI) in claim 7 for the menufacture of a medicant for treating septic shock in humans.

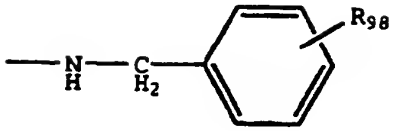
9. The compound of formula (VI) in claim 7 wherein the 1H-indole-3-acetamide is (i) substituted at the 1 position with a -(CH2)-(carbocyclic radical) or -(CH2)-(heterocyclic) radical, and (ii) substituted with an acidic group at the 4 or 5 position; with the proviso that when the 1H-indole-3-acetamide nucleus is substituted at the 4 position the acidic group is selected from the group:

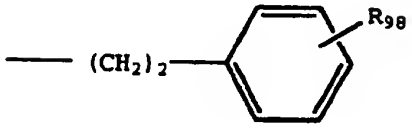
$$-O-CH_2-R_{98},$$
$$-S-CH_2-R_{98},$$
$$-NH-CH_2-R_{98} \text{ and}$$
$$-CH_2-CH_2-R_{98};$$

and when the 1H-indole-3-acetamide nucleus is substituted at the 5 position the acidic group is selected from the group:









- O - $(CH_2)_{2-4}$ - R_{98}
- S - $(CH_2)_{2-4}$ - R_{98}
- NH - $(CH_2)_{2-4}$ - R_{98}
- CH_2 - $(CH_2)_{2-4}$ - R_{98}

where acidic group R_{98} is selected from;

- CO_2H
- SO_3H
- $P(O)(OH)_2$

or salts, and ester derivatives of such acidic groups.

or a pharmaceutically acceptable salt or prodrug thereof, for use in treating septic shock in humans.

10. A compound selected from the group (A) thru (AA):
(A) 4-[[3-(2-Amino-2-oxoethyl)-2-chloro-1-(phenylmethyl)-1H-indole-5-yl]oxy]butanoic acid,
(B) [3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,
(C) [3-[[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid,
(D) 4-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid,
(E) 4-[[3-(2-Amino-2-oxoethyl)-2-(methylthio)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid,
(F) 5-(4-Amino-4-oxobutoxy)-2-(methylthio)-1-(phenylmethyl)-1H-indole-3-acetamide,
(G) [4-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1-H-indol-5-yl]oxy]butanoic acid,
(H) 2-Ethyl-5-(4-hydrazino-4-oxobutoxy)-1-(phenylmethyl)-1H-indole-3-acetamide,
(I) [3-[[3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid,
(J) [3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid monomethyl ester,
(K) [3-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-5-yl]oxy]propyl]phosphonic acid,
(L) [[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-methyl-1H-indol-4-yl]oxy]methyl]acetic acid sodium salt,
(M) [[3-(2-Amino-2-oxoethyl)-1-([1,1'-biphenyl]-2-ylmethyl)-2-methyl-1H-indol-4-yl]oxy]acetic acid sodium salt,
(N) [[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid,
(O) 2-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1H-indol-4-yl]oxy]acetic acid,
(P) 2-Cyclopropyl-5-hydroxy-1-(phenylmethyl)-1H-indole-3-acetamide,
(Q) [3-[[3-(2-Amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid,
(R) [3-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid,
(S) 4-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid,
(T) 3-[4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]propane]sulfonic acid,
(U) 3-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid monomethyl ester,
(V) 2-Bromo-6-chloro-5-methoxy-1-(phenylmethyl)-H-indole-3-acetamide,
(W) 2-Bromo-6-chloro-5-hydroxy-1-(phenylmethyl)-H-indole-3 acetamide,
(X) 4-[[3-(2-Amino-2-oxoethyl)-2-bromo-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]butanoic acid,

(Y) 3-[4-[[3-(2-Amino-2-oxoethyl)-6-chloro-1-(phenylmethyl)-1H-indol-5-yl]oxy]propyl]phosphonic acid,
(Z) 4-Allyl-2-ethyl-5-hydroxy-1-(phenylmethyl)-1H-indole-acetamide,
(AA) 2-[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-5-yl]oxy]methyl]benzoic acid;
and pharmaceutically acceptable salts and prodrug derivatives of each of the compounds (A) thru (AA).

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 94 30 2666

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
A	US-A-3 259 622 (T.-Y. SHEN ET AL.) * the whole document * ---	1-10	C07D209/22 C07D209/24 C07D401/06
X,D	US-A-3 242 163 (L.H. SARETT ET AL.) * claims; example 56 * ---	1-10	A61K31/405
X	BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE 1962 , PARIS FR pages 1060 - 1068 M. JULIA ET AL. 'Recherches en série indolique. VI. Sur quelques tryptamines substituées.' *CAS RN 93879-42-6, 95618-47-6, 97077-43-5, 97077-80-0, 97077-79-7* * table II * ---	7	
A	ARZNEIMITTEL FORSCHUNG. DRUG RESEARCH vol. 30(II), no. 8A , 1980 , AULENDORF DE pages 1314 - 1325 K.-H. BOLTZE ET AL. 'Chemische Struktur und antiphlogistische Wirkung in der Reihe der substituierten Indol-3-essigsäuren.' * the whole document * ---	1-10	
	-/--		

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

C07D
A61K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	22 July 1994	Bosma, P

EPO FORM 1503 03.82 (P04C07)

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 94 30 2666

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	CHEMICAL ABSTRACTS, vol. 112, no. 24, 11 June 1990, Columbus, Ohio, US; abstract no. 223181s, A.H. KAHNS ETA L. 'Kinetics of hydrolysis of indomethacin and indomethacin ester prodrugs in aqueous solution.' page 407 ; *CAS RN 6264-33-1* * abstract * & ACTA PHARMACEUTICA NORDICA vol. 1, no. 6 , 1989 , STOCKHOLM pages 327 - 336 ---	1-10	
X	JOURNAL OF MEDICINAL CHEMISTRY vol. 20, no. 10 , 1977 , WASHINGTON US pages 1344 - 1346 A. ANDREANI ET AL. 'Nonsteroidal antiinflammatory agents. 2. Synthesis and biological activity of 2-chloroindolecarboxylic acids.' *compound 11* ---	1,2,4,7	TECHNICAL FIELDS SEARCHED (Int.Cl.5)
X	BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE 1965 , PARIS FR pages 1411 - 1417 M. JULIA ET AL. 'Recherches en série indolique. XIII. Sur quelques méthoxy-5 et -6 tryptamines.' *page 1412: N-benzyl-3-indolylacetamide* -----	7	

EPO FORM 1503 03.82 (P04C09)

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-C-

MEANINGFUL SEARCH NOT POSSIBLE ON THE BASIS OF ALL CLAIMS

The subject matter of the present application is so broad that a complete search is not possible on economic grounds.
(See Guidelines for Examination in the EPO, Part B, Chapter III.2).
Therefore the search has been based on the examples (Rule 45 EPC).